

HUMIRA® (adalimumab)

for Ulcerative Colitis

Gastrointestinal Drugs Advisory Committee

August 28, 2012



Abbott

CI-001

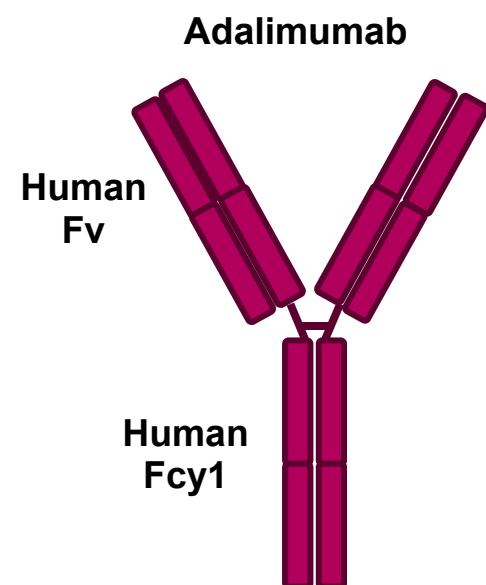
Introduction

John Medich, PhD

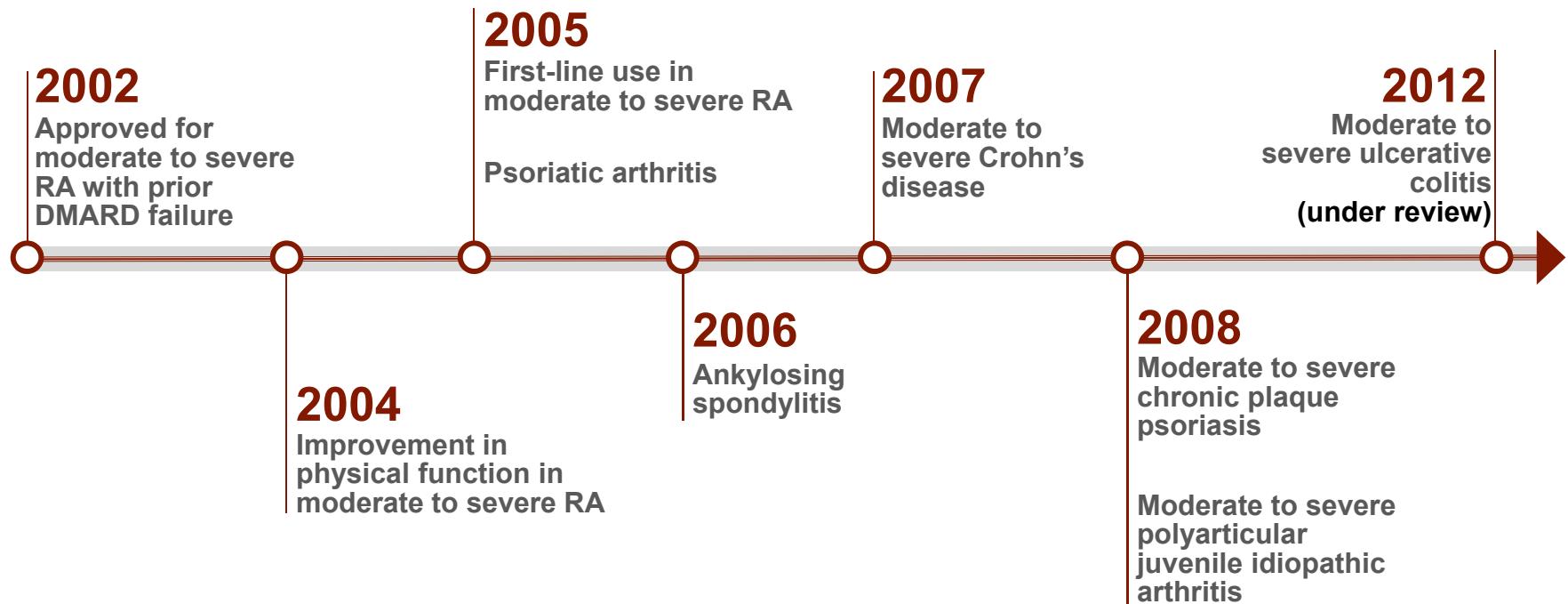
Divisional Vice President,
Immunology Clinical Development
Abbott Laboratories Inc.

HUMIRA® (adalimumab)

- Recombinant fully human monoclonal IgG1 antibody
 - Binds specifically to soluble and membrane-bound TNF- α
 - Leads to decrease in a variety of inflammatory cytokines
- Self-administered subcutaneously
 - Single-use prefilled syringe or pen
 - Dosed every other week
(weekly in some patients)
 - Half-life ~2 weeks



HUMIRA® (adalimumab) FDA Approvals



Global Experience

- Approved in 90 countries for multiple indications
- Cumulative worldwide exposure:
~2 million patient-years since December 2002
 - More than 300,000 patient-years in Crohn's disease

EU Ulcerative Colitis Indication

Humira is indicated for treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

Approved April 2012

CI-006

US Proposed Indication in UC

Humira is indicated for reducing signs and symptoms, and achieving clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.

Proposed Dosage and Administration

- Day 1: 160 mg
- Day 15: 80 mg
- Day 29: 40 mg eow
 - Treatment should only be continued in patients who have responded during the first 8 weeks of therapy
 - For patients who respond and then lose their response, consideration may be given to increasing the dosing frequency to 40 mg every week

Adalimumab UC Program Overview

- **2 double-blind, placebo-controlled, randomized trials**
 - 1094 treatment refractory patients
- **Achieved pre-specified endpoints**
 - The primary endpoint of clinical remission
 - Multiple clinically relevant secondary endpoints
- **Open-label extension with data up to 4 years**
 - >60% continuing to receive therapy
 - >300 patients with 3 or more years of treatment

Focus of Sponsor Presentation

- Robustness and meaningfulness of results
- Adequacy of proposed dosing regimen
- Benefit/risk of adalimumab use in ulcerative colitis

Clinical Program Supports Adalimumab in Ulcerative Colitis

- **Two well-controlled Phase III trials, both of which met their primary endpoints**
 - Treatment effects consistently favored adalimumab across multiple endpoints, sensitivity analyses and studies
 - Clinically relevant improvement was demonstrated in multiple measures including signs and symptoms, mucosal healing and quality of life
- **The benefits outweigh the known risks of adalimumab therapy**

Presentation Agenda

Introduction

John Medich, PhD

Divisional Vice-President, Abbott

Disease Background

Subrata Ghosh, MD, MBBS

Regional Clinical Department Head

Department of Medicine, University of Calgary

Clinical Efficacy

Roopal Thakkar, MD

Project Director, Immunology, Abbott

Safety

Andrea Best, DO, MPH

Senior Medical Director

Immunology Product Safety, Abbott

Benefit/Risk

Roopal Thakkar, MD

Clinical Perspective

William Sandborn, MD

Chief, Division of Gastroenterology

University of California San Diego School of Medicine

Conclusion

John Medich, PhD

Disease Background

Subrata Ghosh, MBBS, MD, FRCPC, FRCP, FRCPE

Professor of Medicine,
Chairman, Department of Medicine,
University of Calgary, CANADA

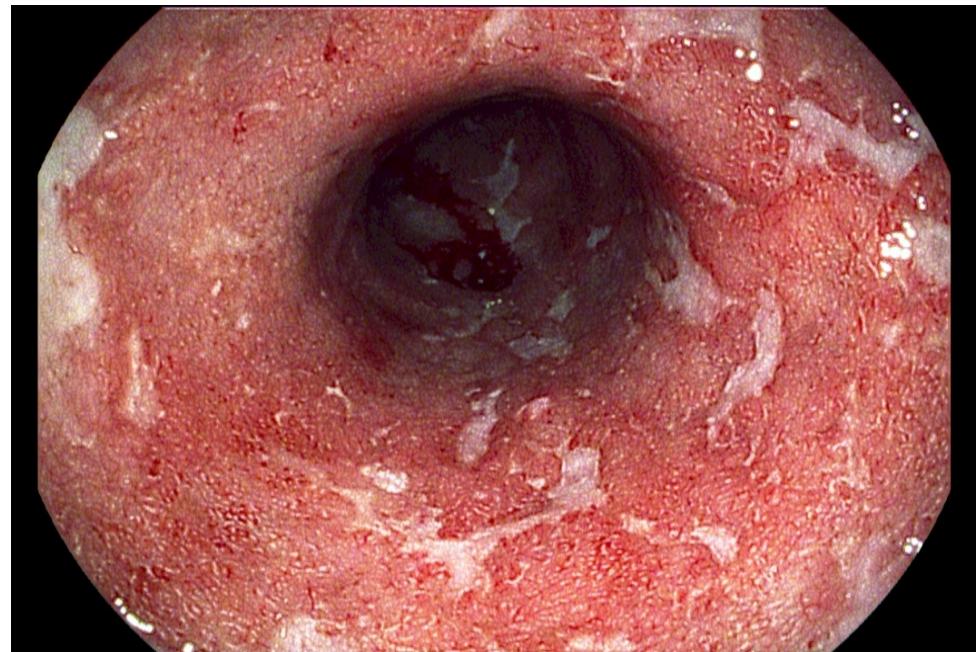
Ulcerative Colitis Background

- **Ulcerative colitis is the most frequent form of IBD in adults¹**
- **Chronic, debilitating disease affecting approximately 700,000 people in the US²**
- **Median age of 35y at diagnosis³**
- **Patient quality of life is poor**
- **Many patients will fail existing therapy**

1. Danese S, Fiocchi C. *N Engl J Med.* 2011.
2. Logan L, Bowlus CL. *Autoimmun Rev.* 2010.
3. Loftus EV. *Gastroenterology.* 2004.

Clinical Features of UC

- Bloody diarrhea
- Urgency, tenesmus
- Abdominal pain
- Fecal incontinence
- Fever
- Weight loss
- Extra-intestinal manifestations (such as arthritis, pyoderma gangrenosum, uveitis)

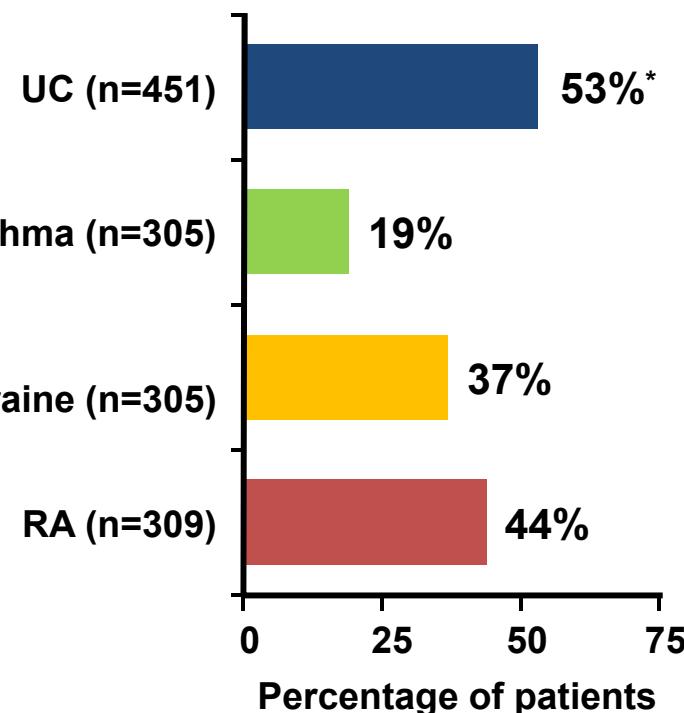


Danese S, Fiocchi C. *N Engl J Med.* 2011.

Walmsley et al. *Gut.* 1998.

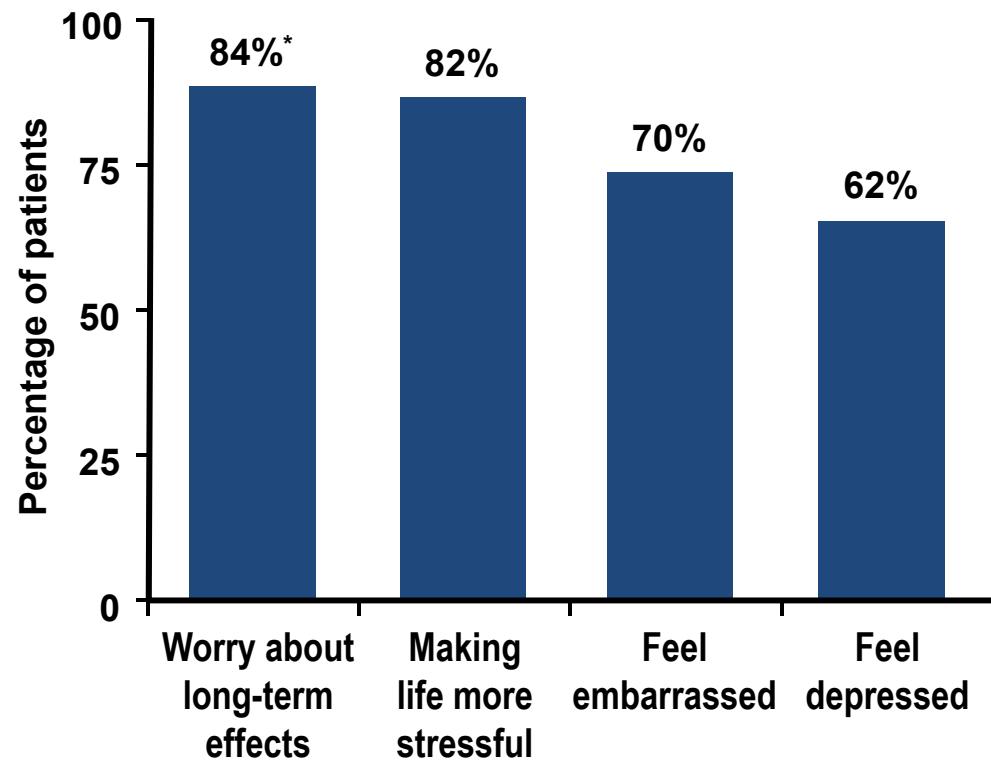
Ulcerative Colitis Has a Significant Impact on Patient Quality of Life

Proportion of patients who feel their condition was controlling their lives



*p<0.05 vs other chronic conditions

Psychological Impact of Ulcerative Colitis
N=451

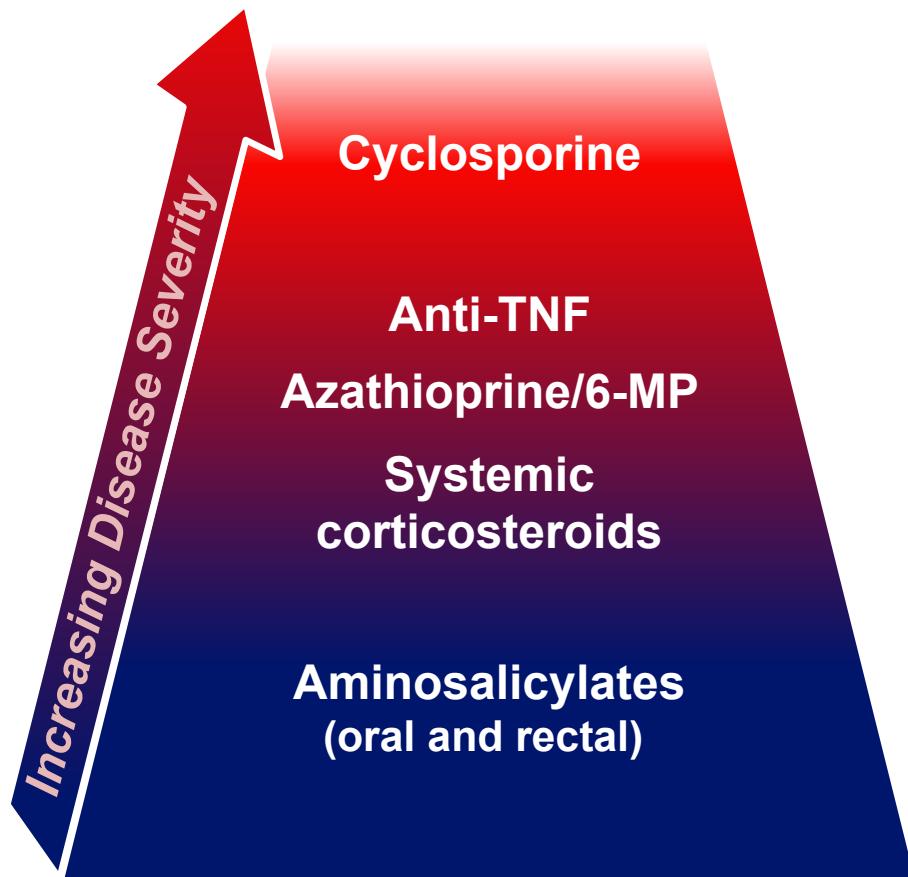


UC Assessment Aligns with Mayo Score¹

Parameter	Score				Full Mayo Score (FMS)
	0	1	2	3	
Stool frequency	Normal for patient	1-2 more than normal	3-4 more than normal	≥5 more than normal	
Rectal bleeding	None	Streaks less than 50% of time	Obvious blood most of the time	Blood alone passed	
Physician's global assessment	Normal	Mild	Moderate	Severe	
Endoscopy findings	Normal/inactive	Mild disease	Moderate disease	Severe disease	

¹Schroeder KW, et al. *N Engl J Med.* 1987;317:1625–9.

Pharmacologic Approach to UC

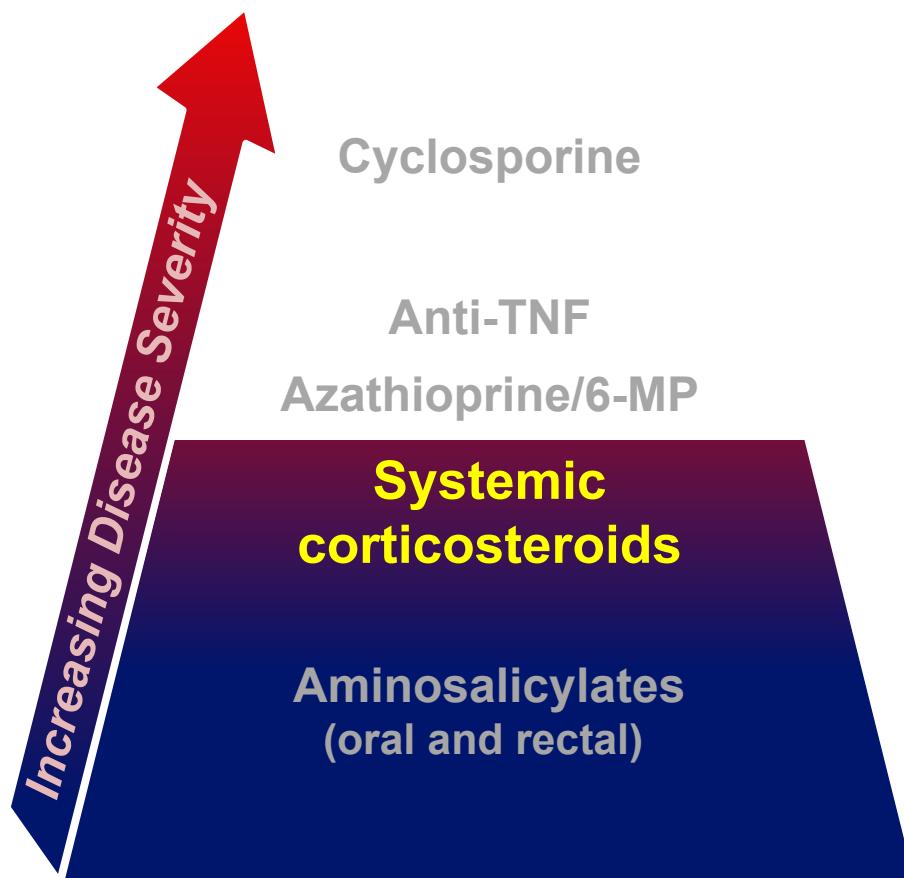


Adapted from Hanauer SB. *Aliment Pharmacol Ther.* 2008.

CM-018

Pharmacologic Approach to UC

Corticosteroids



- Effective for induction of response and remission^{1,2}
- Not appropriate for maintenance therapy
- Patients requiring corticosteroids are at higher risk of colectomy
- Significant adverse events such as infections, cushingoid features, glaucoma, psychiatric disturbances, osteoporosis, hyperglycemia, accelerated atherogenesis, adrenal insufficiency²

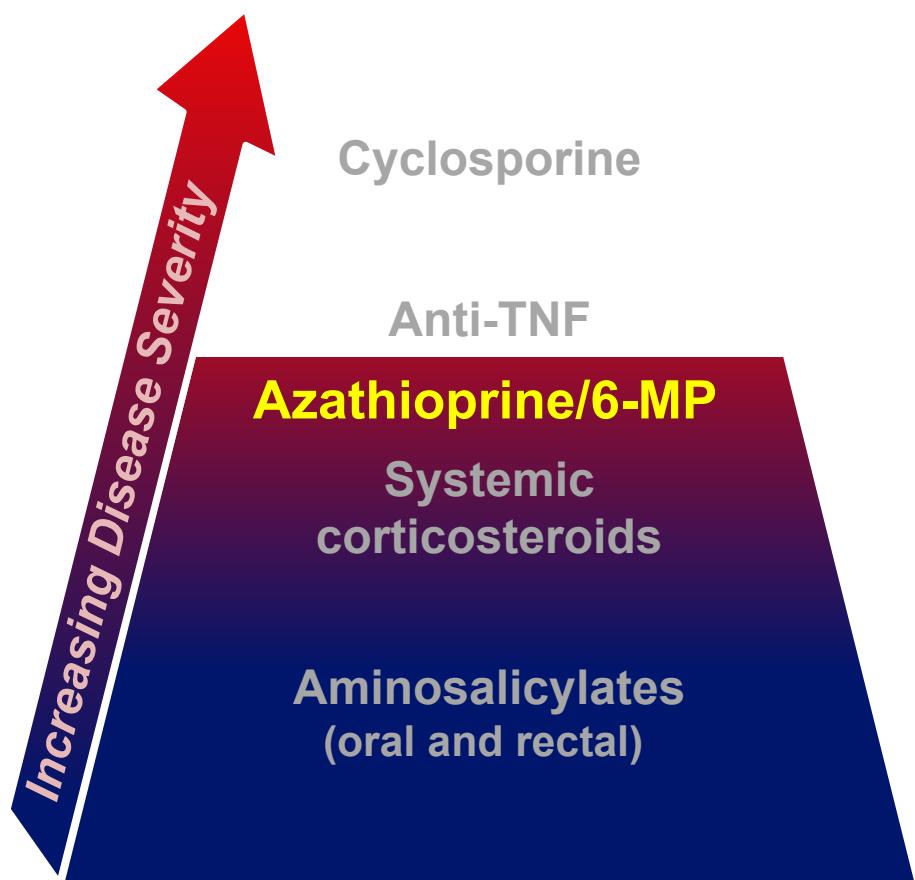
Adapted from Hanauer SB. *Aliment Pharmacol Ther.* 2008.

1. Faubion WA Jr et al. *Gastroenterology* 2001.

2. Kornbluth A, et al. *Am J Gastroenterol.* 2010.

Pharmacologic Approach to UC

Azathioprine/6-MP



Adapted from Hanauer SB. *Aliment Pharmacol Ther.* 2008.

- Used for maintenance of remission^{1,2}
- Not effective for induction of remission¹
- Increased risk of lymphoma (hazard ratio of lymphoproliferative disorders 5.28 (95%CI 2.01–13.9))³
- Skin cancer⁴
- Bone marrow suppression²
- Serious infections⁵
- Hepatotoxicity⁶
- Pancreatitis²

1. Gisbert JP et al. *Aliment Pharmacol Ther.* 2009.

2. Kornbluth A, et al. *Am J Gastroenterol.* 2010.

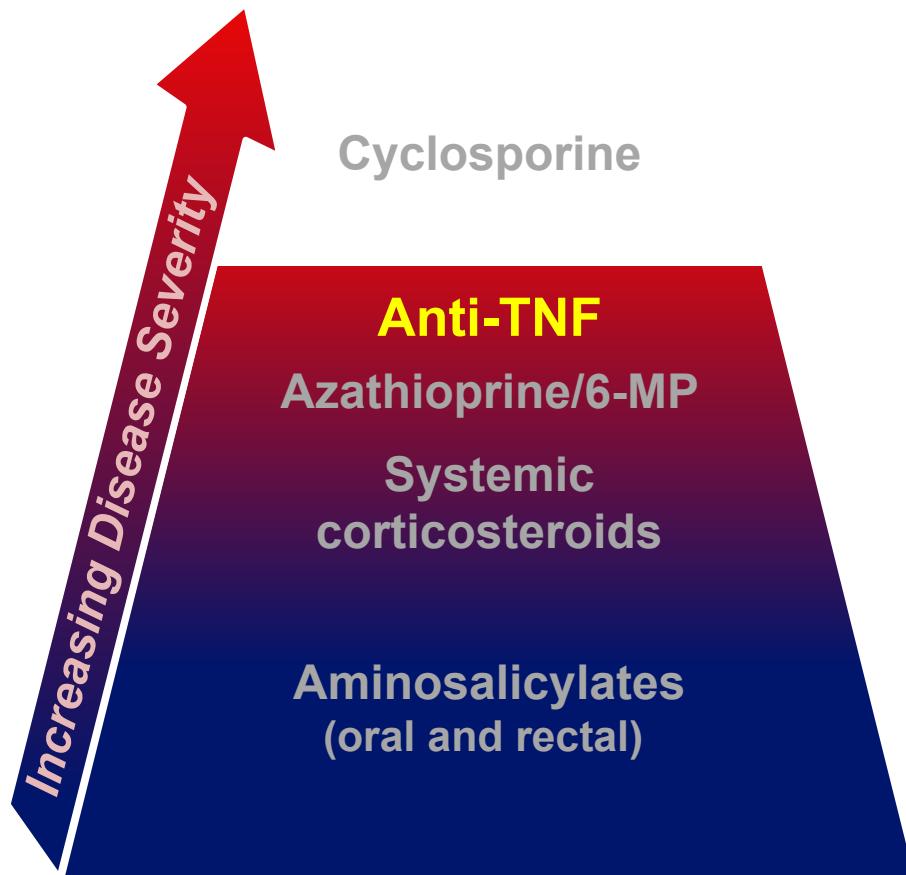
3. Beaugerie et al. *Lancet.* 2009.

4. Peyrin-Biroulet L et al. *Gastroenterology.* 2011.

5. Colombel et al. *N Engl J Med.* 2010.

6. Leong RW et al. *Expert Opin Drug Saf.* 2008.

Pharmacologic Approach to UC Anti-TNF



Adapted from Hanauer SB. *Aliment Pharmacol Ther.* 2008.

- Infliximab effective for patients who are steroid refractory or steroid dependent despite adequate doses of a thiopurine, or who are intolerant to these medications¹
- Loss of response (34%-59% of patients)^{2,3}
- IV route of administration may have limitations
 - Need for pre-medication (55%-75%)⁴⁻⁶
 - Need to travel to infusion centers

1. Kornbluth A, et al. *Am J Gastroenterol.* 2010.

2. Rutgeerts et al. *N Engl J Med.* 2005.

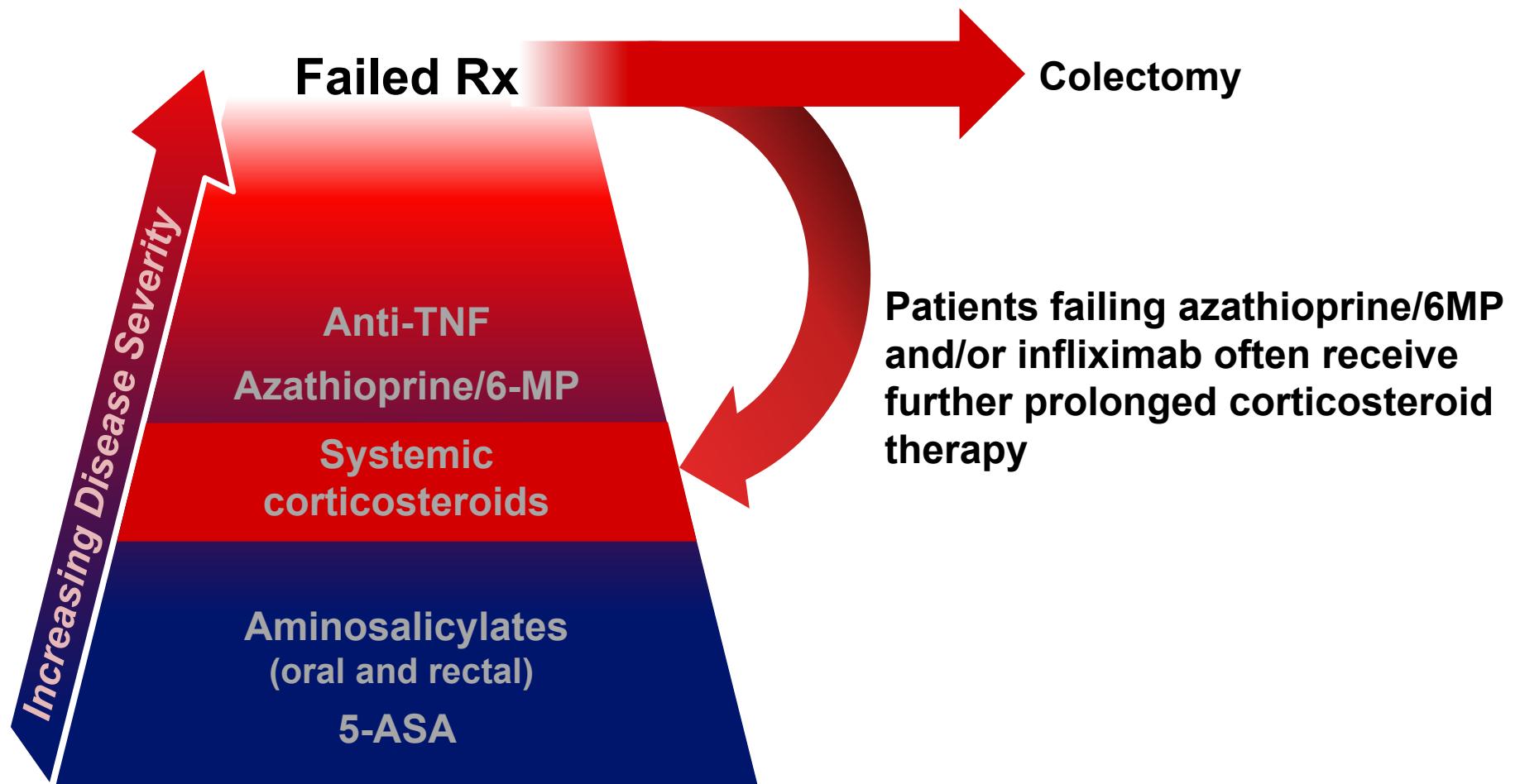
3. Oussalah A et al. *Am J Gastroenterol.* 2010.

4. Ducharme et al. *Can J Gastroenterol.* 2010.

5. Zabana et al. *Aliment Pharmacol Ther.* 2010.

6. Ducharme et al. *Frontline Gastroenterology.* 2011.

Pharmacologic Approach to UC Approach to Advanced Disease



Adapted from Hanauer SB. *Aliment Pharmacol Ther*. 2008.

CM-022

Complications Associated With Colectomy and Pouch in Patients With Ulcerative Colitis

Complication ^{1, 2}	Rate (%)
Non-chronic pouchitis	28.4
Chronic pouchitis	10.9
Small bowel obstruction	17.8
Loss of fecundity	47.9
Mortality	2.3 0.7 (Elective) vs 5.4 (Emergent)

- Other complications reported in the literature

- Abnormal bowel pattern: 3-10 stools/24 hrs³
 - Fecal incontinence ~20%⁴
- Long-term pouch failure 8.5%⁴

1. Leonard et al. 7th Congress of ECCO, 16-18 February 2012, Barcelona, Spain
2. Kaplan et al. *Gastroenterology*. 2008.
3. Sagar PM, et al. eds. *Inflammatory Bowel Diseases*. 2003.
4. Huetting HE et al. *Dig Surg*. 2005.

Ulcerative Colitis: Hospitalizations

- **Hospitalizations are common**
 - 34% of US patients with moderate to severe UC hospitalized per year¹
 - Patients may have multiple hospitalizations: 70 events per 100 patients annually¹
- **Disruptive to patients' lives**
 - 15% of US employees with UC had received short-term disability benefits in one year²
- **High economic impact on public health care system³**
 - Direct medical costs for patients with moderate to severe UC estimated to be \$26,000/year¹
- **Available therapies for UC have not decreased hospitalization rates in the US between 1970 – 2004^{4,5}**

1. Cohen RD et al. *Submitted to ACG 2012*
2. Gibson TB et al. *J Occup Environ Med.* 2008.
3. Cohen RD et al. *Aliment Pharmacol Ther.* 2010.
4. Bewtra M et al. *Clin Gastroenterol Hepatol.* 2007.
5. Sonnenberg. *J Clin Gastroenterol.* 2008.

Ulcerative Colitis: Disease Background Summary

- Chronic, debilitating disease affecting approximately 700,000 people in the US
- Interference with everyday life
- Available therapies, including colectomy have considerable limitations
- Hospitalization rates remain frequent and contribute significantly to disease burden
- High unmet need

Efficacy

Roopal Thakkar, MD

Project Director, Immunology
Abbott Laboratories Inc.

CE-026

Agenda

- **Disease activity measurements**
- **Study population**
- **Study designs**
- **Endpoint descriptions**
- **Study patients**
- **Primary and secondary endpoints**
- **Supportive analyses**
- **Exposure/response analyses**

Disease Activity Assessments Were Based on the Mayo Score¹

Parameter	Score				Full Mayo Score (FMS)
	0	1	2	3	
Stool frequency	Normal for patient	1-2 more than normal	3-4 more than normal	≥5 more than normal	
Rectal bleeding	None	Streaks less than 50% of time	Obvious blood most of the time	Blood alone passed	
Physician's Global Assessment	Normal	Mild	Moderate	Severe	
Endoscopy findings	Normal/inactive	Mild disease	Moderate disease	Severe disease	

¹Schroeder KW, et al. *N Engl J Med.* 1987;317:1625–9.

Disease Activity Assessments Were Based on the Mayo Score¹

Parameter	Score				Partial Mayo Score (PMS)
	0	1	2	3	
Stool frequency	Normal for patient	1-2 more than normal	3-4 more than normal	≥5 more than normal	
Rectal bleeding	None	Streaks less than 50% of time	Obvious blood most of the time	Blood alone passed	
Physician's Global Assessment	Normal	Mild	Moderate	Severe	
Endoscopy findings	Normal/inactive	Mild disease	Moderate disease	Severe disease	

¹Schroeder KW, et al. *N Engl J Med.* 1987;317:1625–9.

Key Inclusion Criteria

Studies 826/827

- **Moderately to severely active UC, as defined by a Mayo score of 6 to 12 points despite concurrent therapy**
 - Endoscopy subscore of 2 or 3 (moderate or severe disease)
- **Prior and/or concurrent treatment with oral corticosteroids and/or immunosuppressants**
 - Note: Patients who failed only aminosalicylates were not eligible
- **Previous treatment with an anti-TNF agent permitted in patients who lost response or were intolerant (Study 827 only)**

Key Exclusion Criteria

Studies 826/827

- Intravenous corticosteroids within 14 days**
- Disease limited to the rectum
(ulcerative proctitis)**

Agenda

- Disease activity measurements
- Study population
- **Study designs**
- Endpoint descriptions
- Study patients
- Primary and secondary endpoints
- Supportive analyses
- Exposure/response analyses

Clinical Development Program

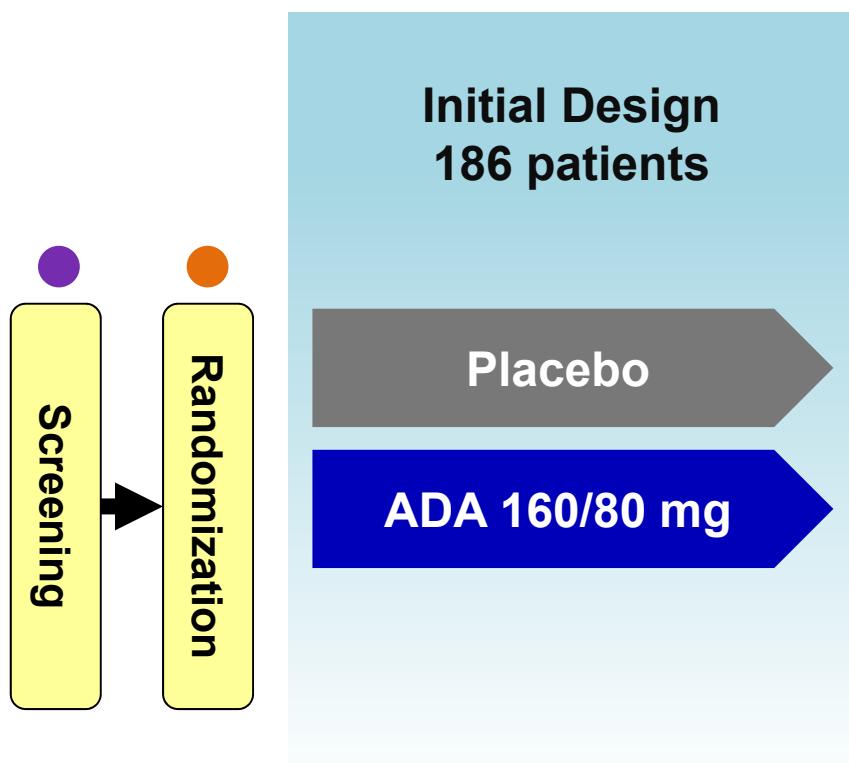
Phase 3 studies in adult patients with moderate to severe UC

Study 826:
Randomized, controlled, double-blind,
8-week induction study, with open-label
phase through Week 52

Study 827:
Randomized, controlled, double-blind study
– Induction and maintenance through
Week 52

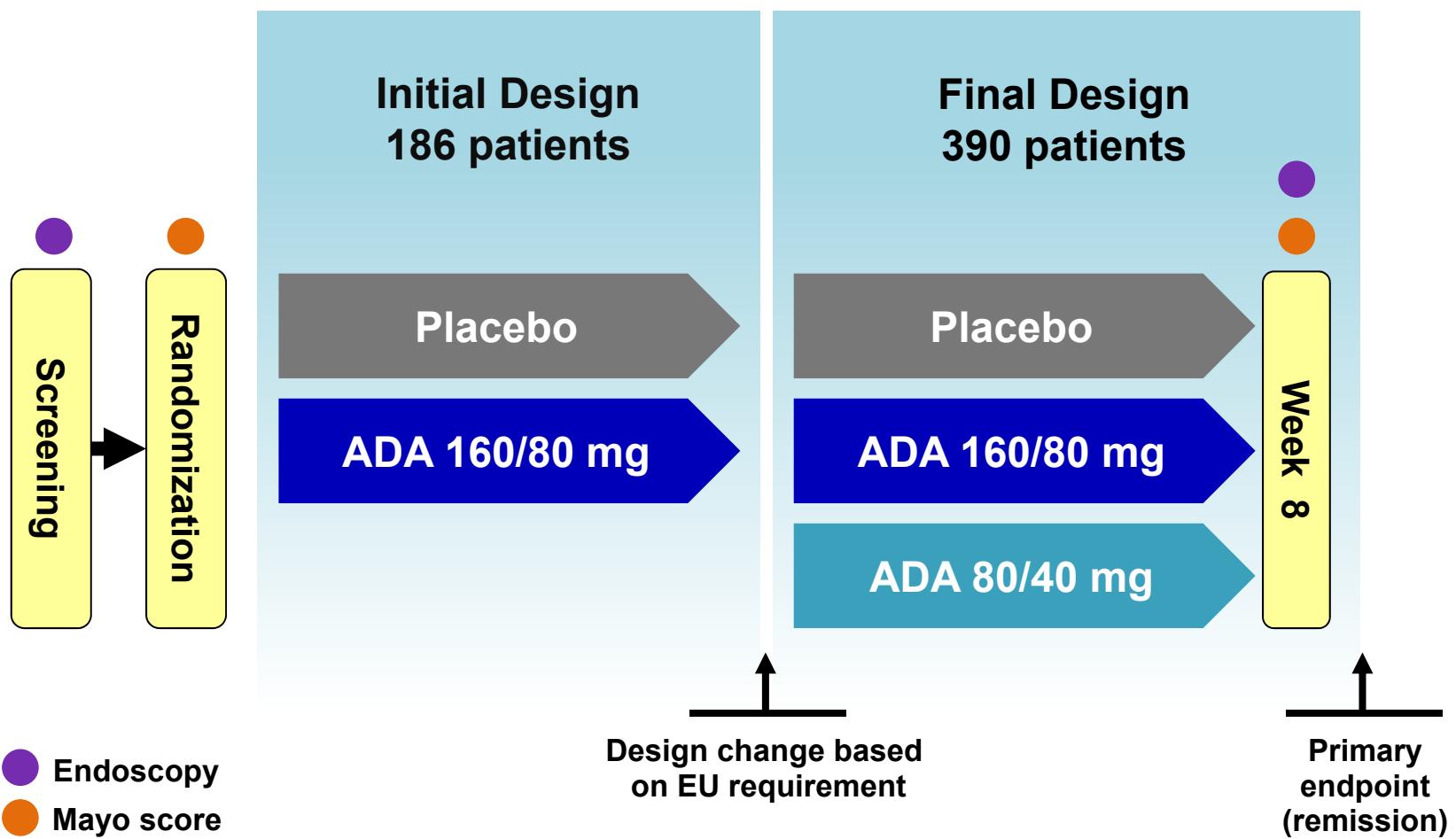
Study 223:
Open-label, long term,
extension study

Study 826 (Induction)



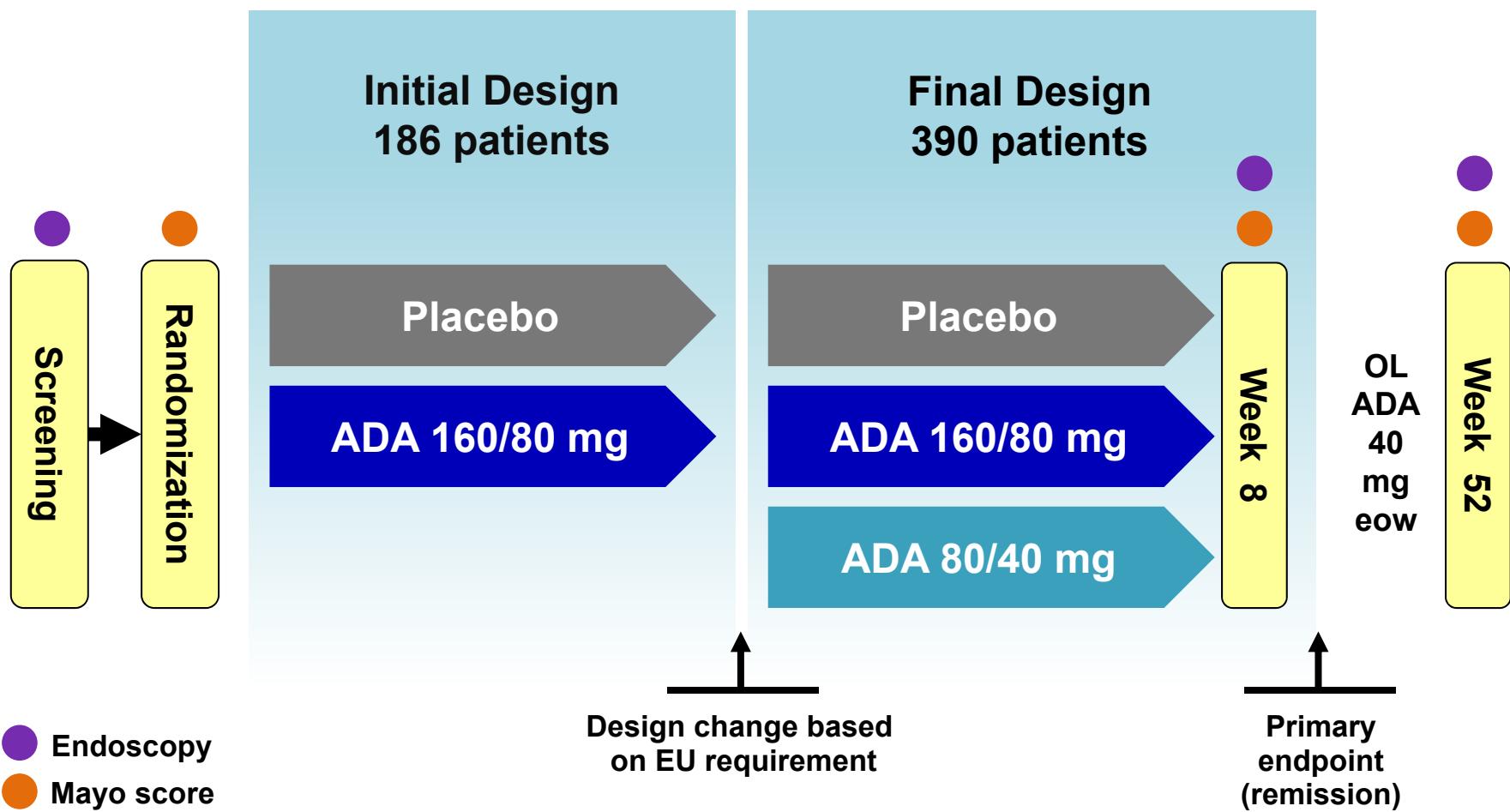
- Endoscopy
- Mayo score

Study 826 (Induction)



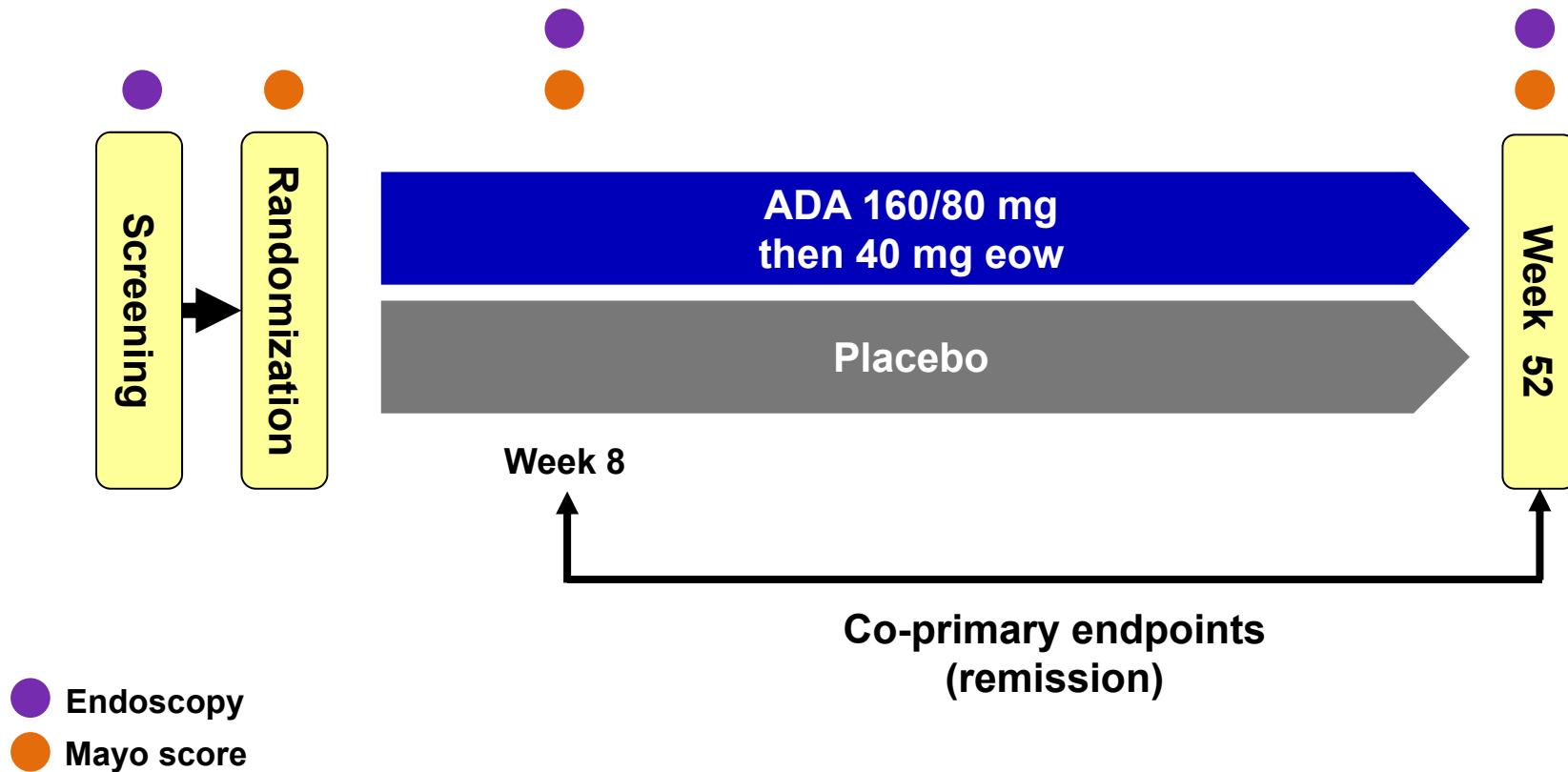
CE-035

Study 826 (Induction)



Study 827 (Induction and Maintenance)

518 Patients

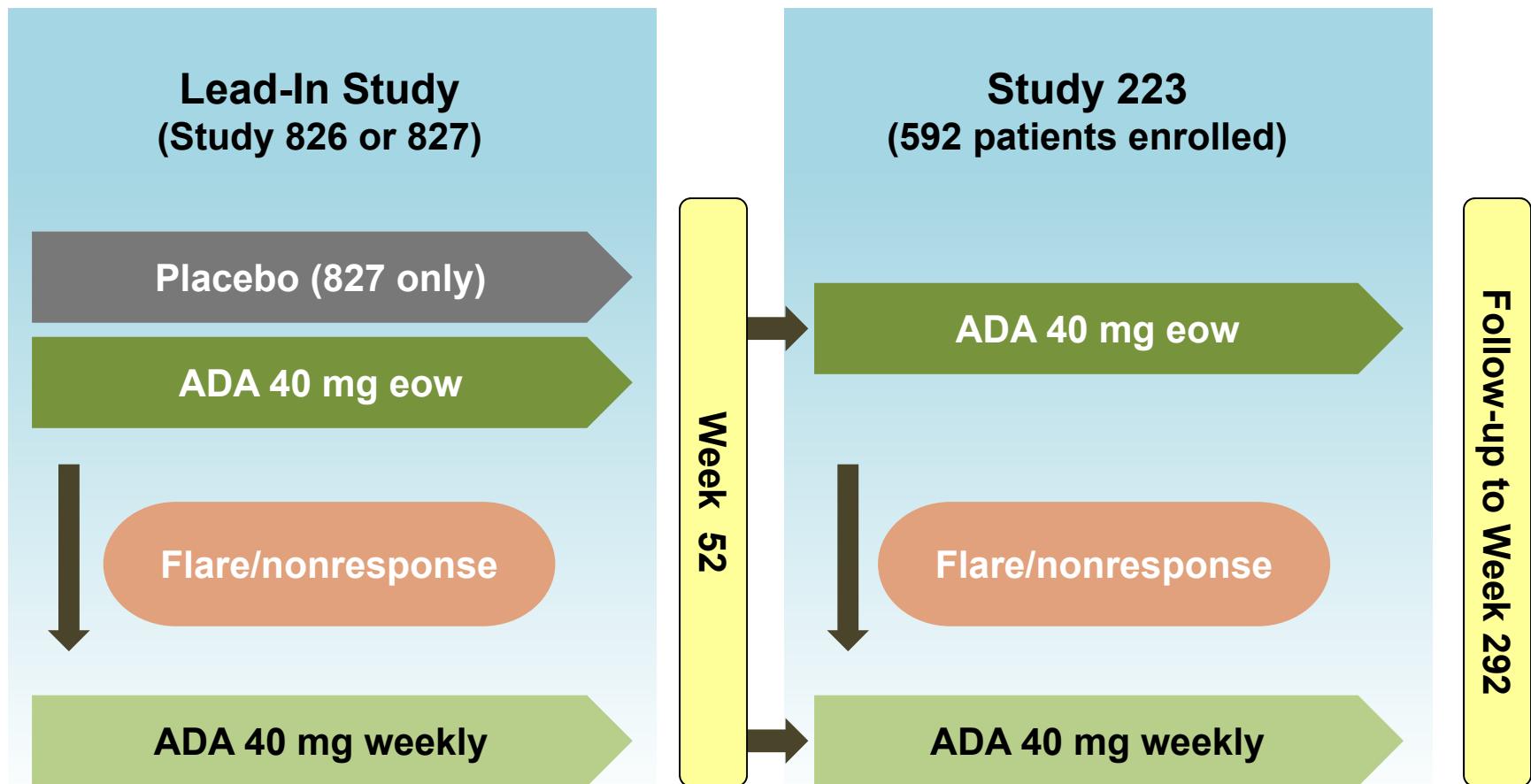


CE-037

Escape Criteria Studies 826/827

- **Inadequate response definitions:**
 - Baseline partial Mayo score of 4 to 7:
Score \geq baseline score on 2 consecutive visits at least 14 days apart
 - Baseline partial Mayo score of 8 or 9:
Score ≥ 7 on 2 consecutive visits at least 14 days apart

Study 223 (Open-Label Extension)



Agenda

- Disease activity measurements
- Study population
- Study designs
- **Endpoint descriptions**
- Study patients
- Primary and secondary endpoints
- Supportive analyses
- Exposure/response analyses

Pre-Specified Efficacy Endpoint Definitions

Term	Definition	
Remission (FMS and PMS)	Mayo score ≤2 with no individual subscore >1	
Response (FMS)	Decrease in Mayo score ≥3 points	and ≥30% from baseline PLUS a decrease in rectal bleeding subscore (RBS) ≥1 or an absolute RBS of 0 or 1
Response (PMS)	Decrease in Partial Mayo score ≥2 points	
Mucosal Healing	Endoscopy subscore of 0 or 1	

Primary Endpoint

Study 826

- **Proportion of subjects with remission at Week 8**
 - First 160/80 mg dose tested first at a significance level of 0.05
 - Then 80/40 mg dose tested at a significance level of 0.05
- **Study considered to be successful if 160/80 mg dose met statistical significance versus placebo**

Primary Endpoints

Study 827

- **Co-primary endpoints**
 - Proportion of subjects with remission at Week 8
 - Proportion of subjects with remission at Week 52
- **Study considered successful if both endpoints met statistical significance at the 0.05 level versus placebo**

Trial Design Characteristics

- Primary endpoints were based on remission
- Both trials required active disease despite steroid and/or immunosuppressant therapy
- Patients with previous anti-TNF exposure were included in Study 827
- Steroid taper not mandated
- All efficacy evaluations occurred when adalimumab levels were at trough

Agenda

- Disease activity measurements
- Study population
- Study designs
- Endpoint descriptions
- **Study patients**
- Primary and secondary endpoints
- Supportive analyses
- Exposure/response analyses

Baseline Characteristics

Study 826

	Placebo N=130	ADA 80/40 N=130	ADA 160/80 N=130
Male (%)	63	60	64
Age (mean, yrs)	39	42	38
CRP (median, mg/L)	3.2	6.4	3.3
Site of UC (% pancolitis)	56	54	46
Disease duration (mean, yrs)	7.5	8.6	8.1
Mayo score (mean)	8.7	9.0	8.8
Any UC-related therapy (%)	96	95	93
Baseline steroids and/or AZA/6MP (%)	82	76	76
Baseline steroids (%)	68	57	55

ITT analysis set

CE-046

Baseline Characteristics

Study 827

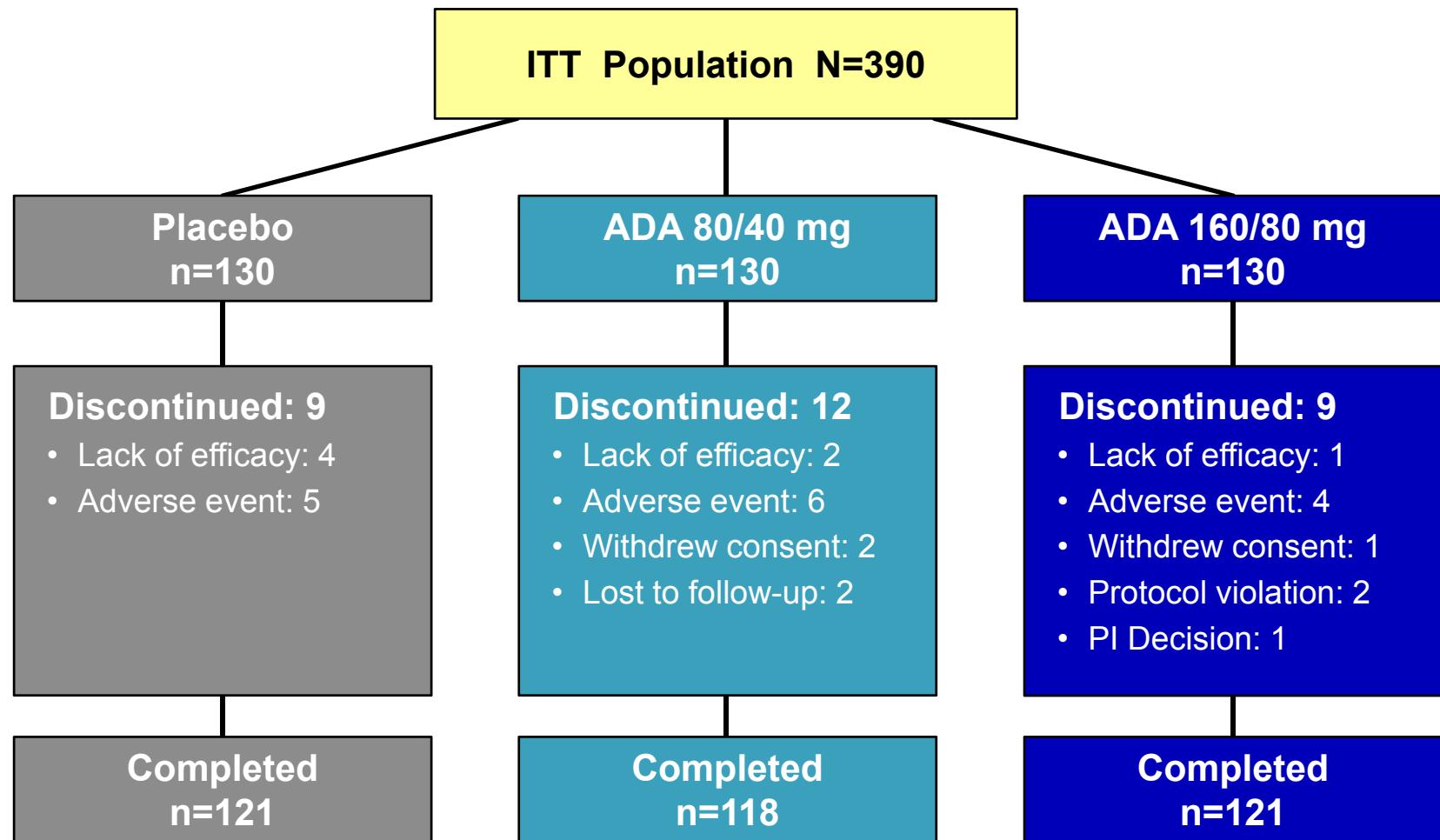
	Placebo N=246	Adalimumab 160/80 N=248
Male (%)	62	57
Age (mean, yrs)	41	40
CRP (median, mg/L)	4.2	4.1
Site of UC (% pancolitis)	49	48
Disease duration (mean, yrs)	8.5	8.1
Mayo score (mean)	8.9	8.9
Any UC-related therapy (%)	89	90
Baseline steroids and/or AZA/6MP (%)	71	78
Prior anti-TNF exposure (%)	41	40

ITT analysis set

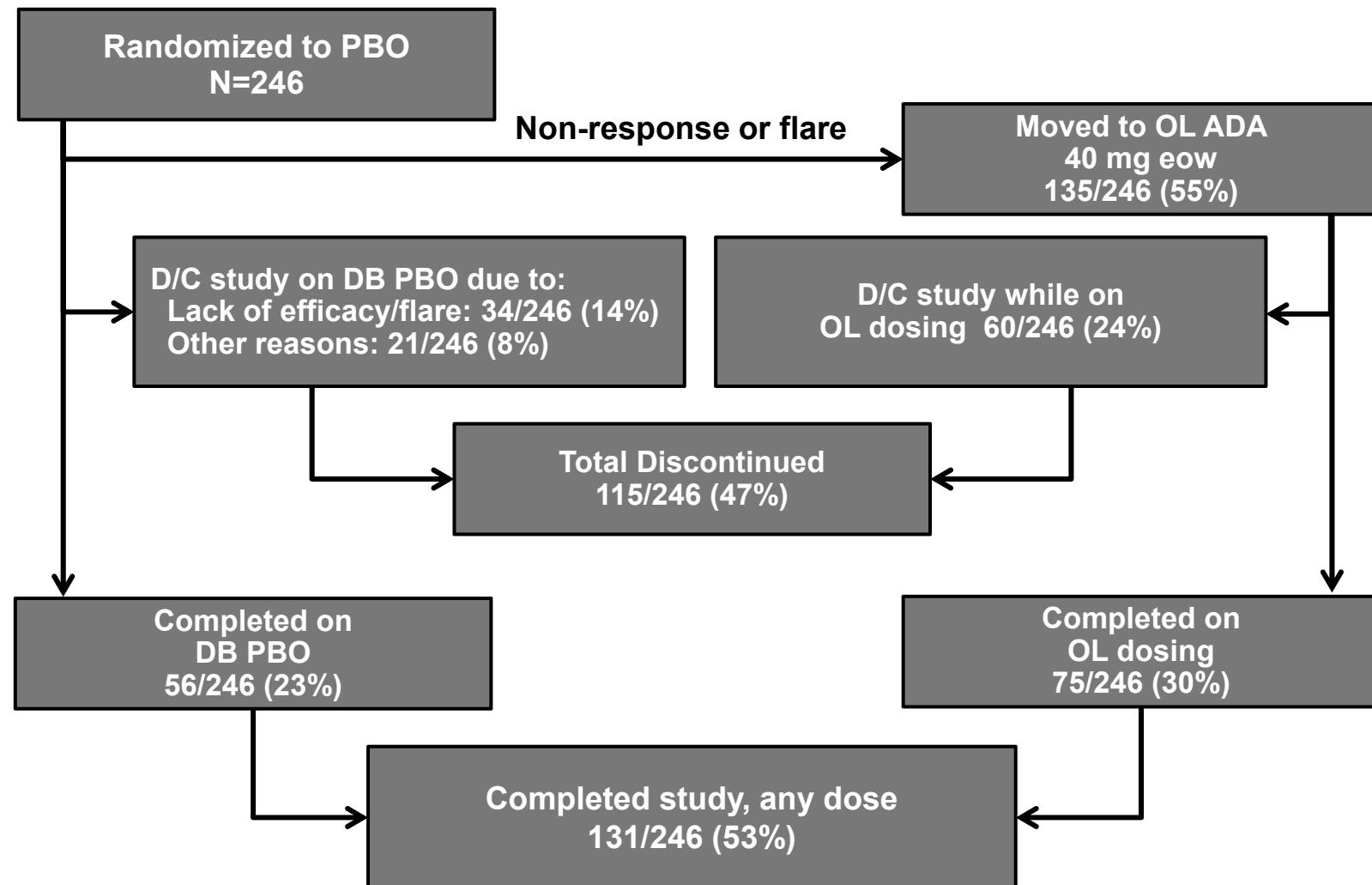
CE-047

Patient Disposition Through Week 8

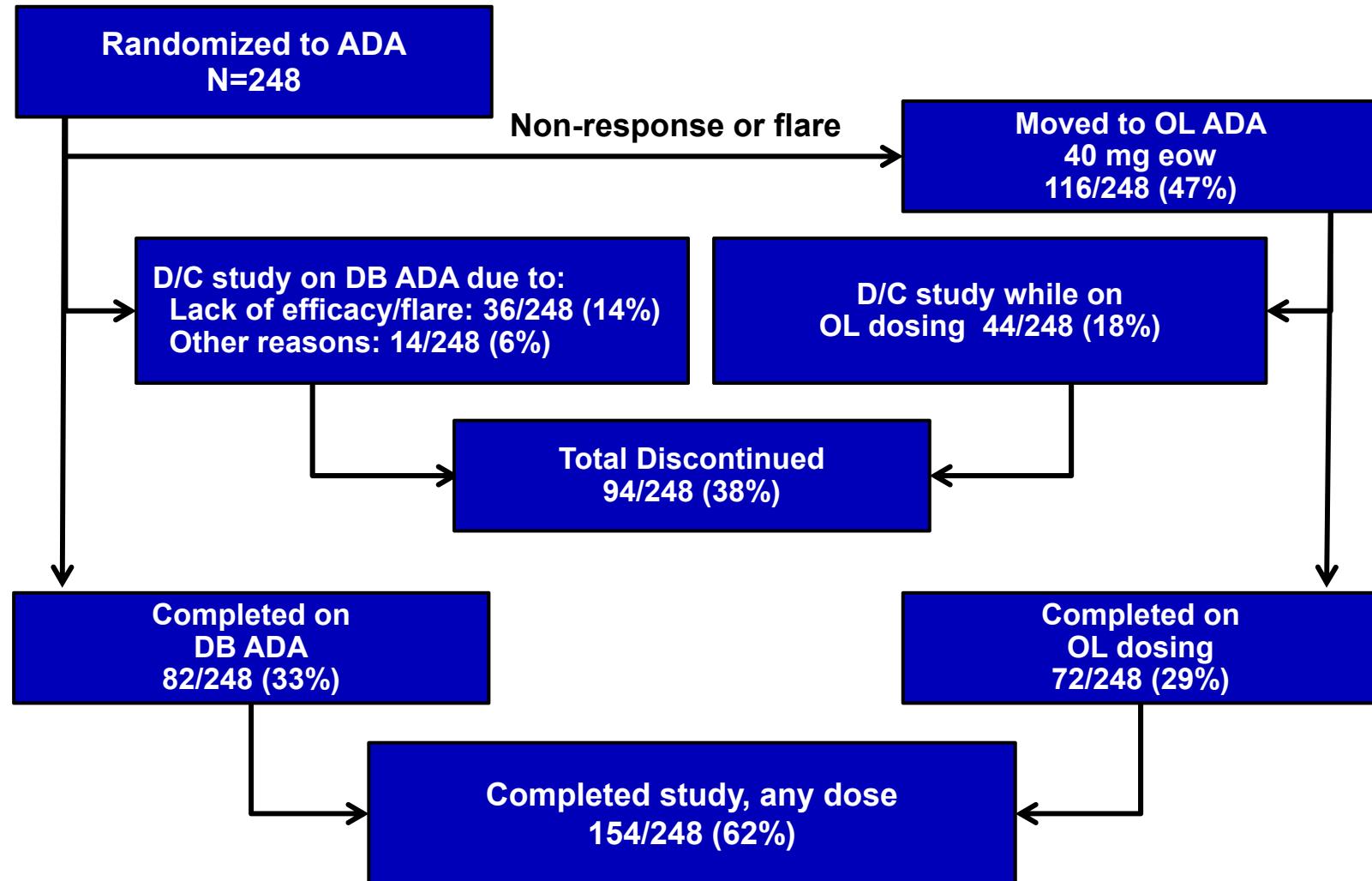
Study 826



Study 827: Placebo Patient Disposition



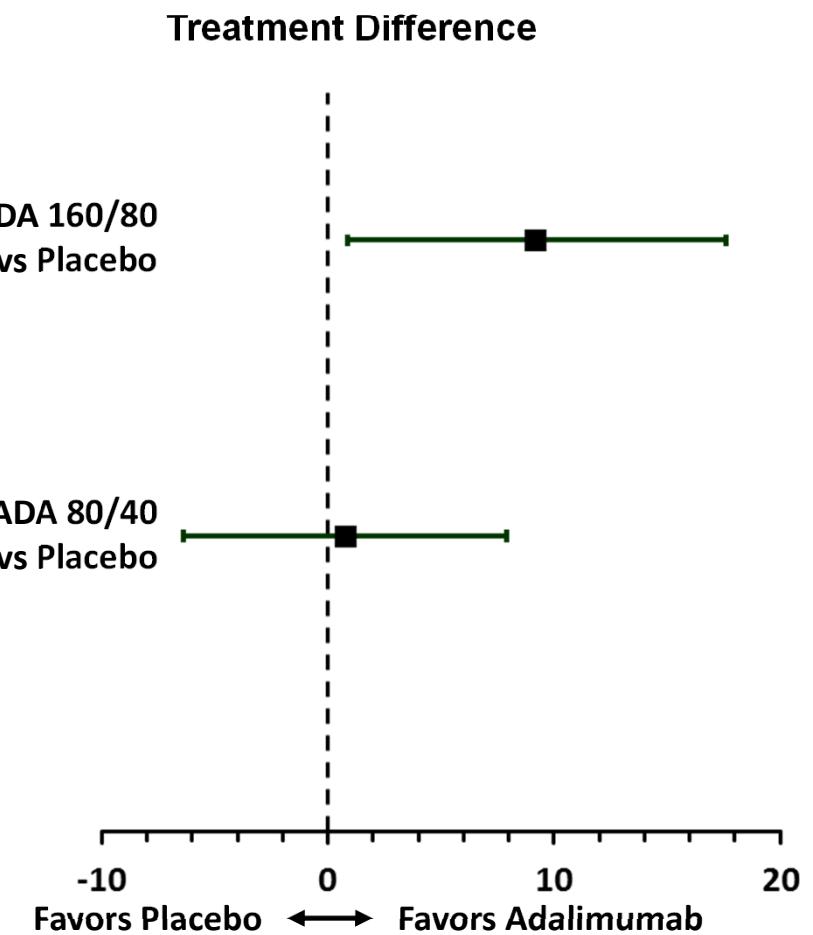
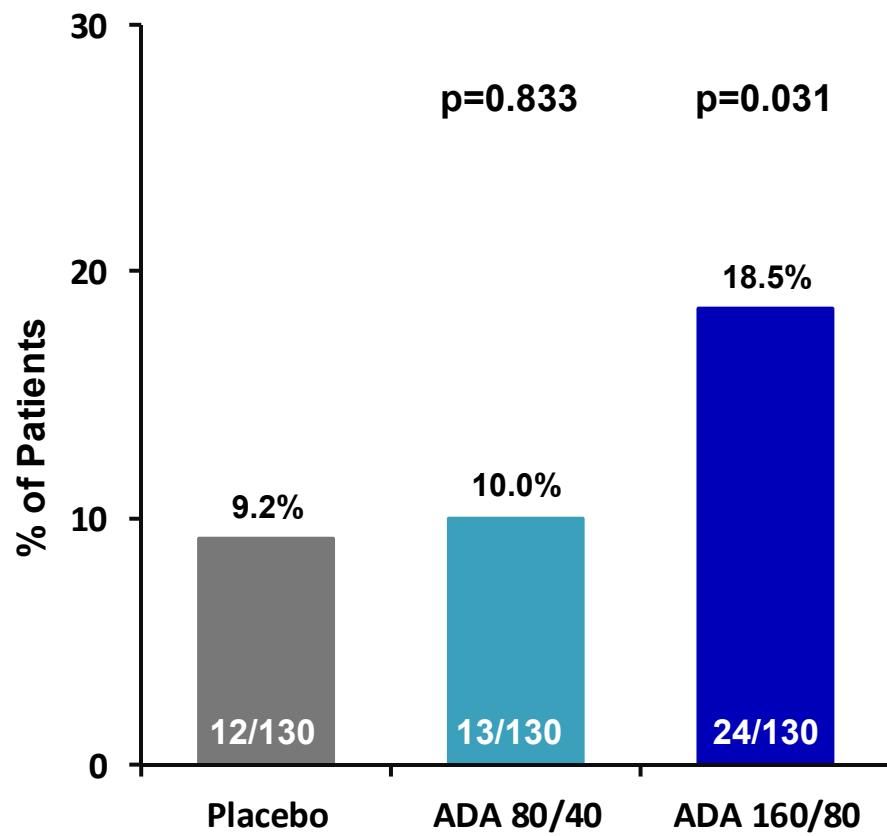
Study 827: ADA Patient Disposition



Agenda

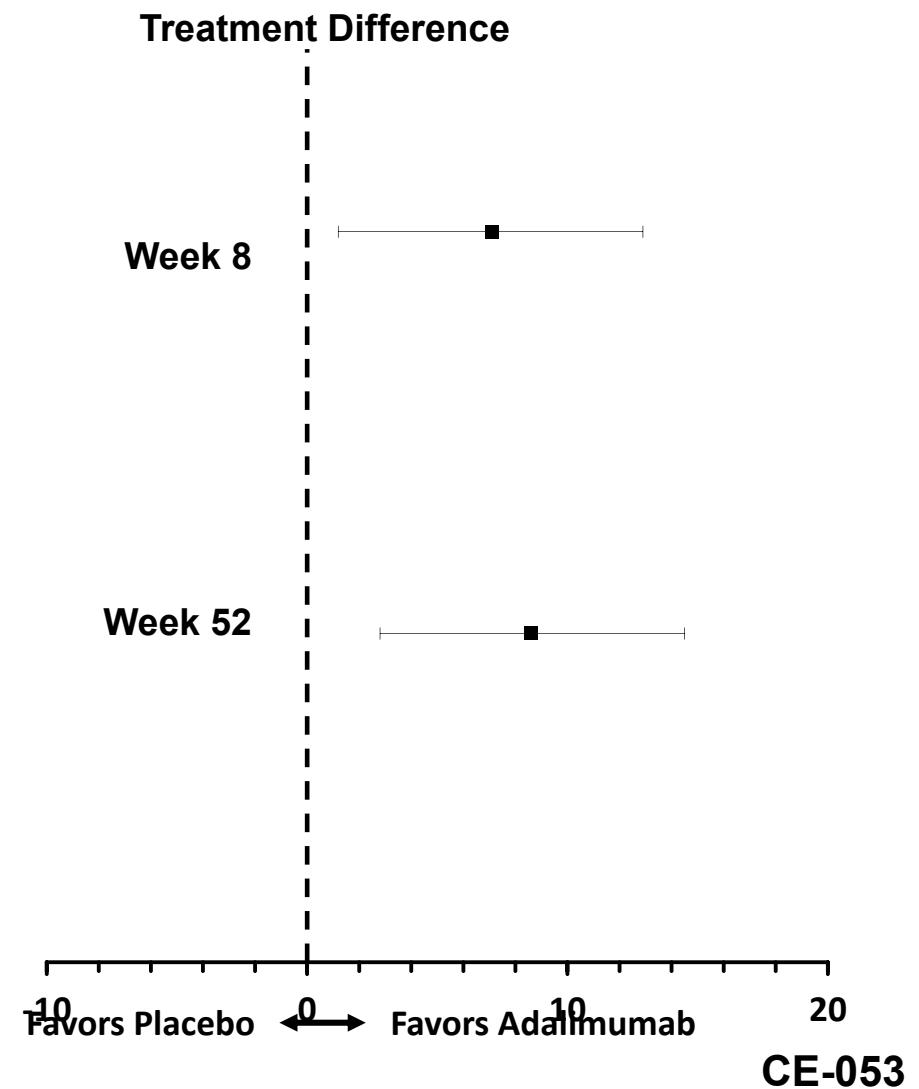
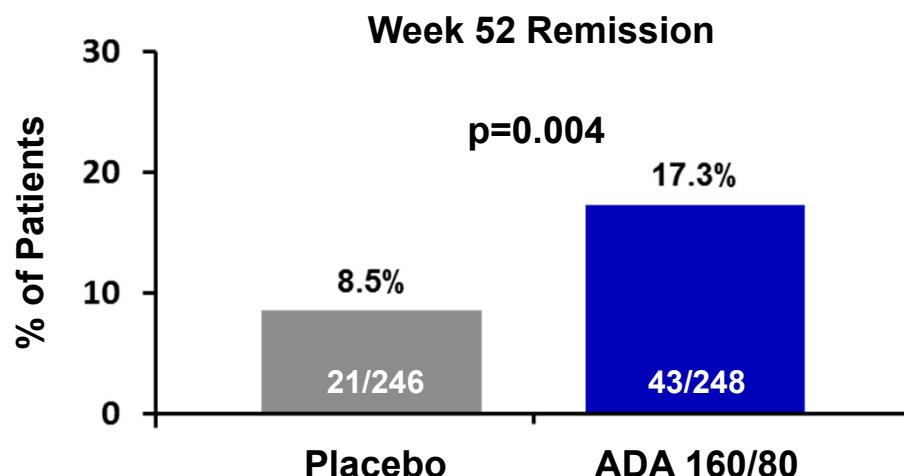
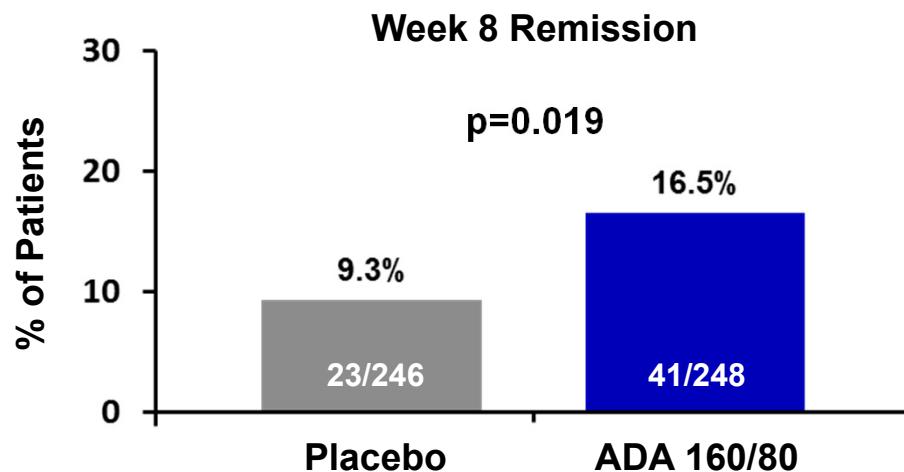
- Disease activity measurements
- Study population
- Study designs
- Endpoint descriptions
- Study patients
- **Primary and secondary endpoints**
- Supportive analyses
- Exposure/response analyses

Primary Endpoint for Study 826: Remission at Week 8

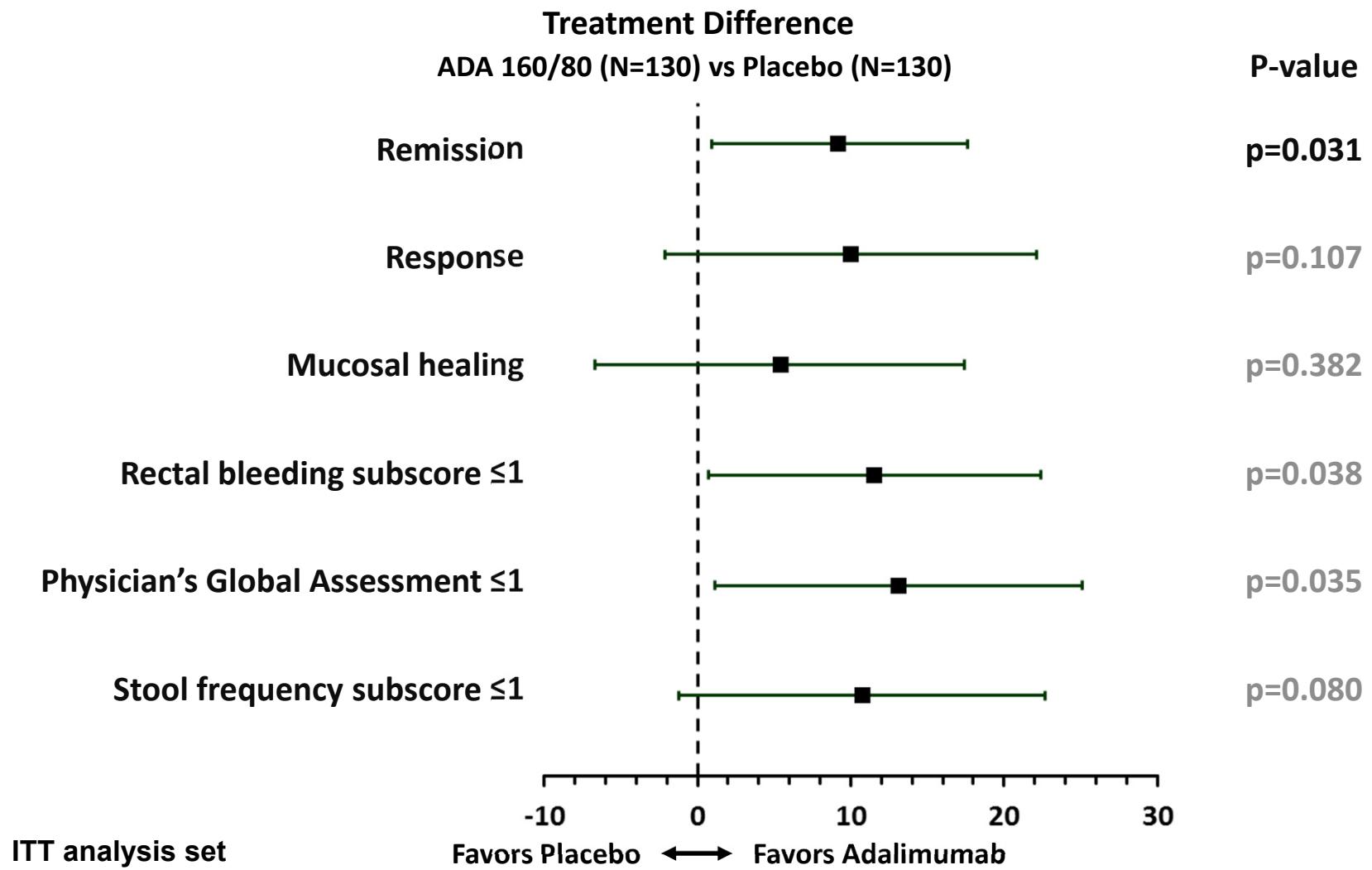


CE-052

Co-Primary Endpoints for Study 827: Remission at Week 8 and at Week 52



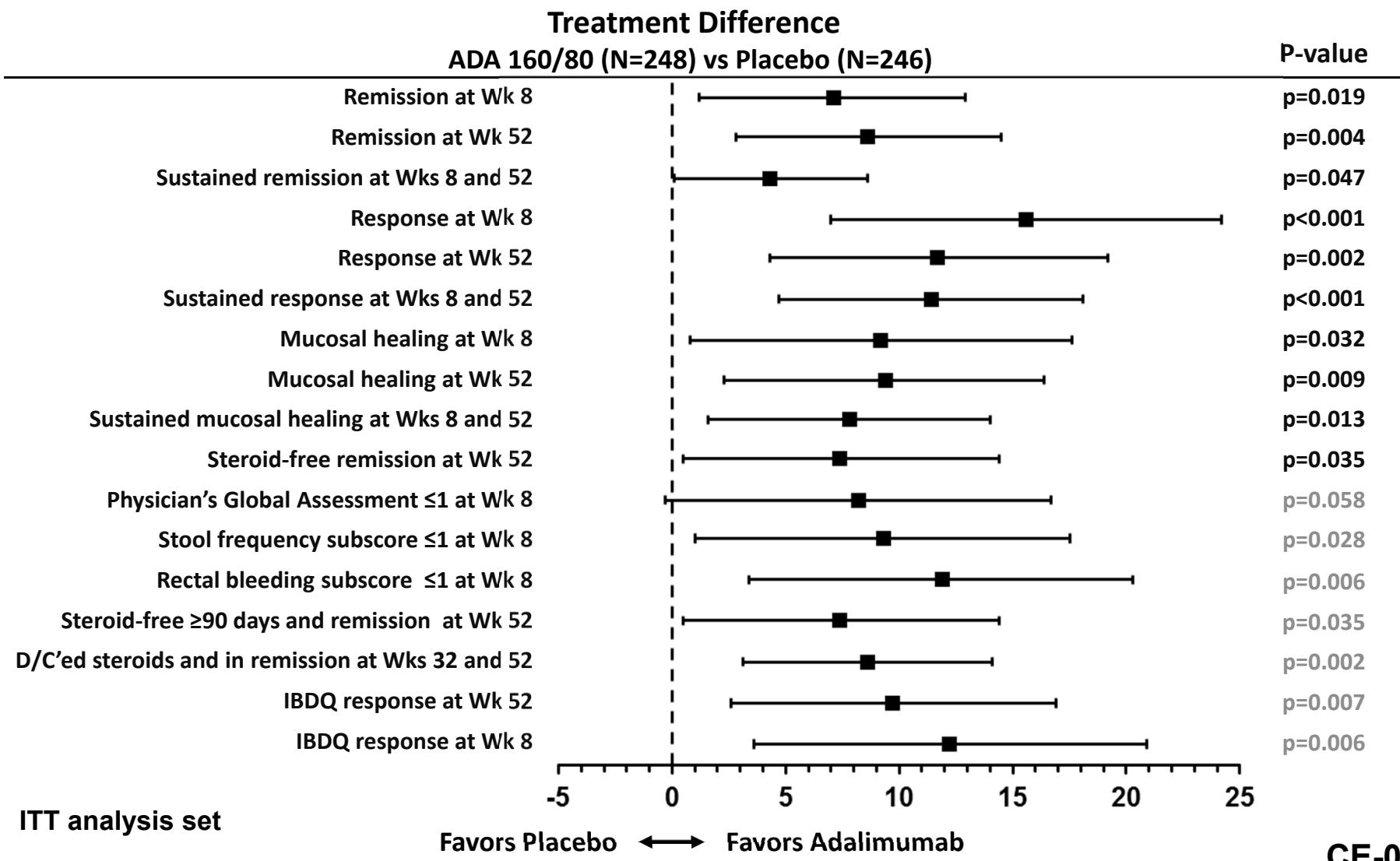
Pre-Specified Primary and Ranked Secondary Endpoints at Week 8 Study 826



CE-054

Pre-Specified Endpoints

Study 827



CE-055

Agenda

- Disease activity measurements
- Study population
- Study designs
- Endpoint descriptions
- Study patients
- Primary and secondary endpoints
- **Supportive analyses**
- Exposure/response analyses

Statistical Analysis of Remission at Week 8

Study 826

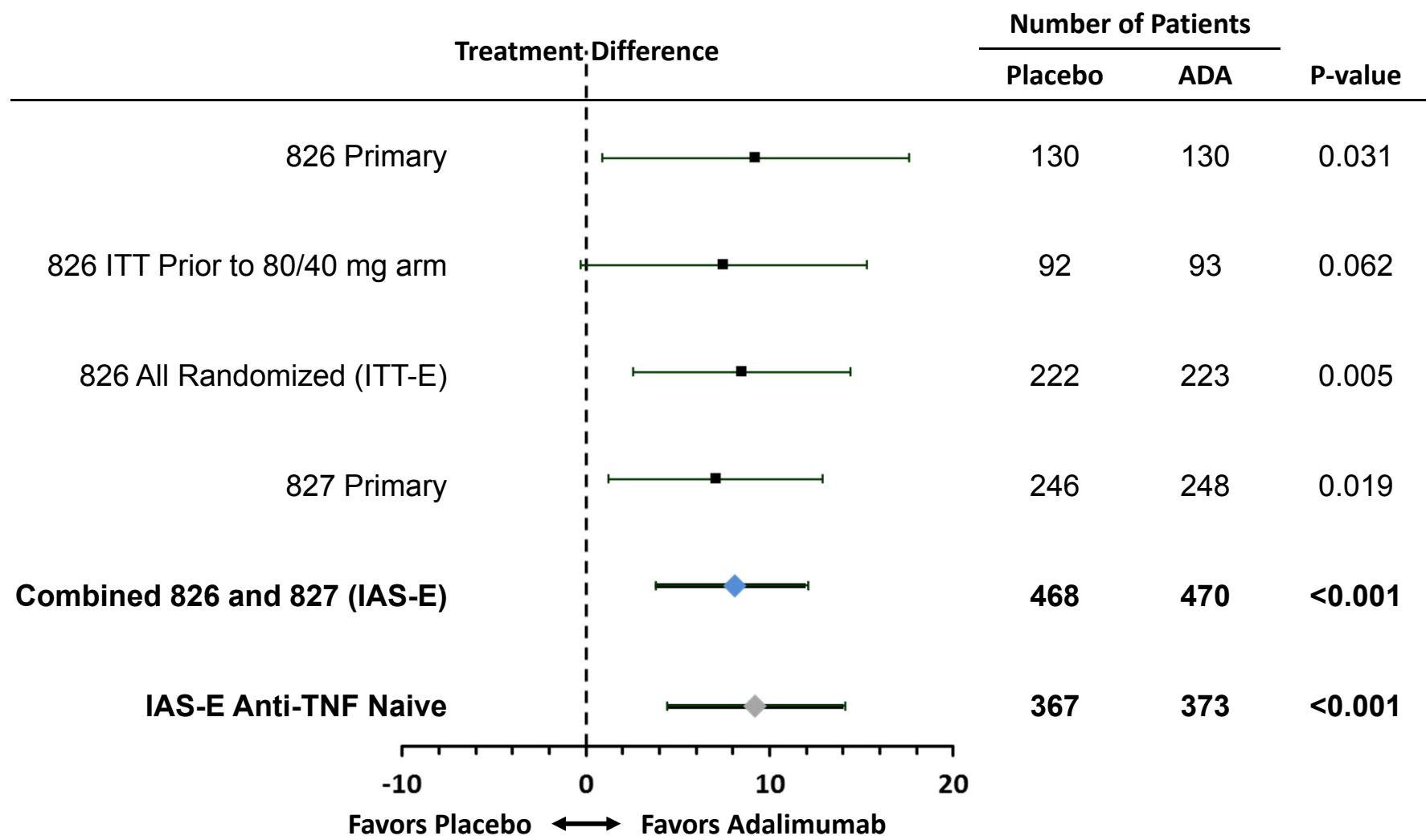
Analysis Methodology		Stratification Variables	P-value
Pre-specified: Chi-squared			0.031
FDA	CMH	BL Mayo score (7 categories)	0.085
	Fisher's exact test		0.047
	CMH	BL Mayo score (4 categories)	0.034
	CMH	BL Mayo score (3 categories)	0.034
	CMH	BL Mayo score (2 categories)	0.028
Abbott	Logistic regression	BL Mayo score (continuous)	0.030
	Logistic regression	BL Mayo score, CRP, and CS use	0.023
	Logistic regression	BL Mayo score, CRP, CS use, and pancolitis	0.016
	Non-parametric ANCOVA	BL Mayo score	0.028

ITT analysis set, ADA 160/80 vs PBO

CE-057

Remission at Week 8

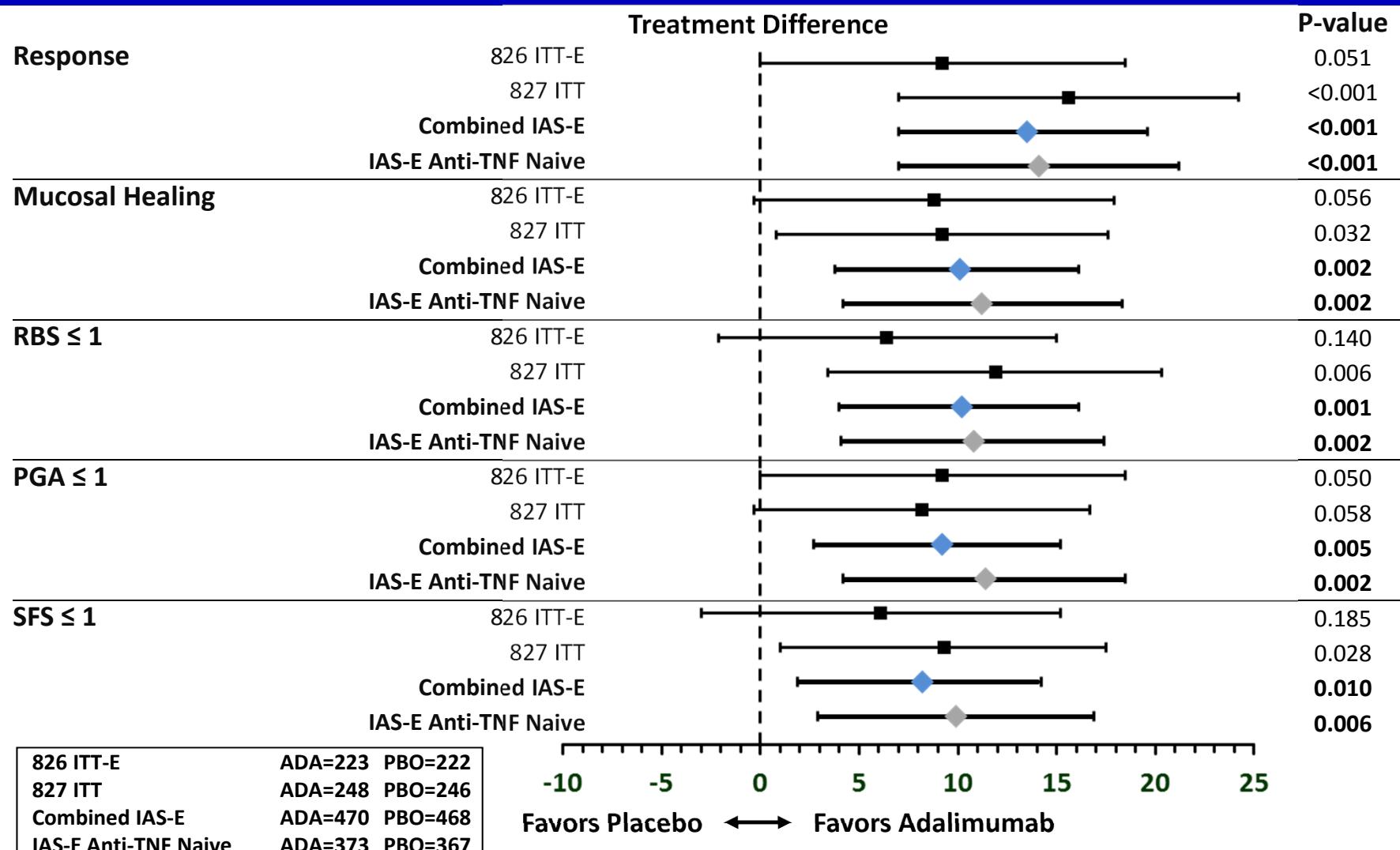
Studies 826/827



CE-058

Additional Endpoints at Week 8

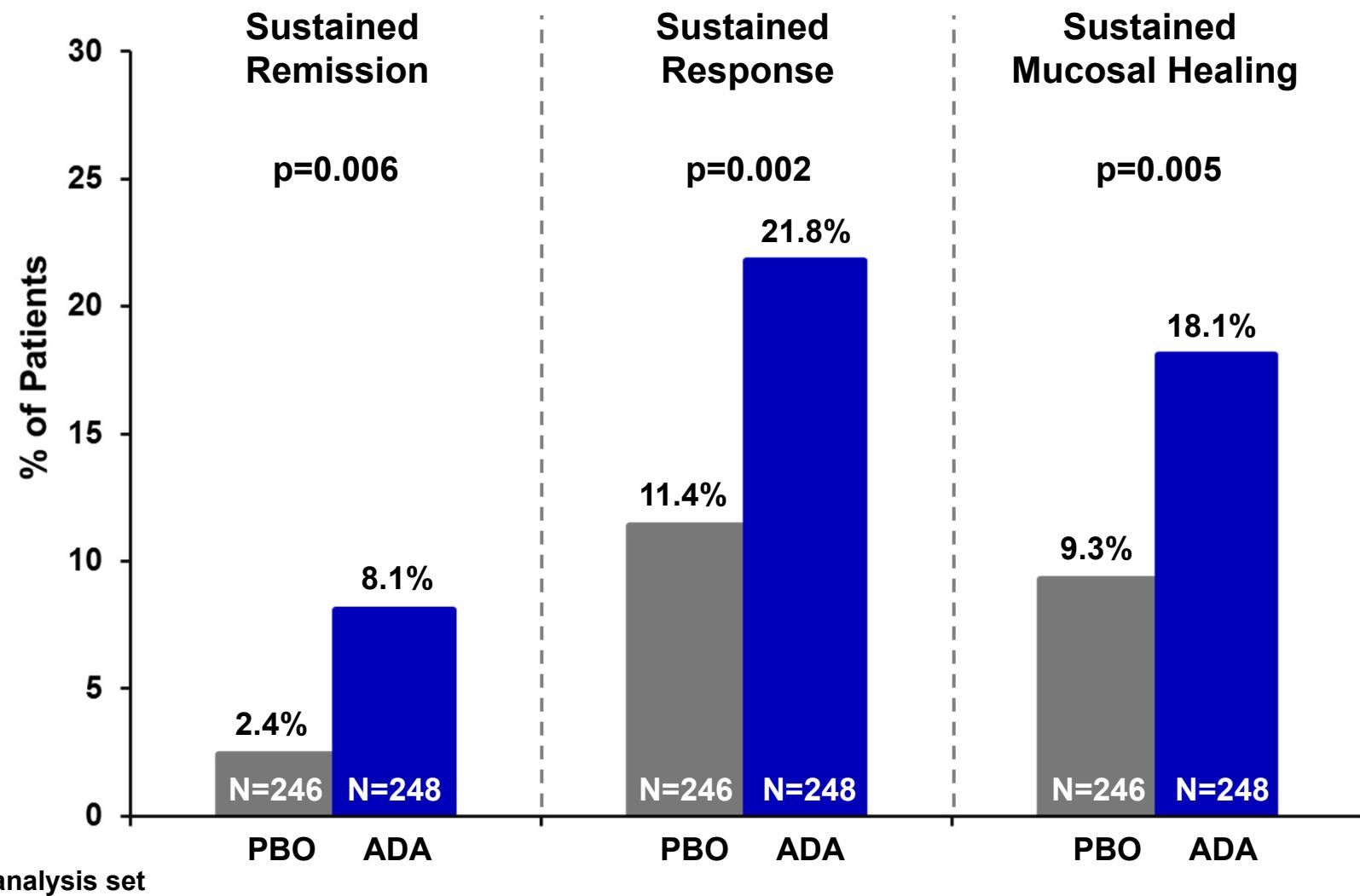
Studies 826/827



CE-059

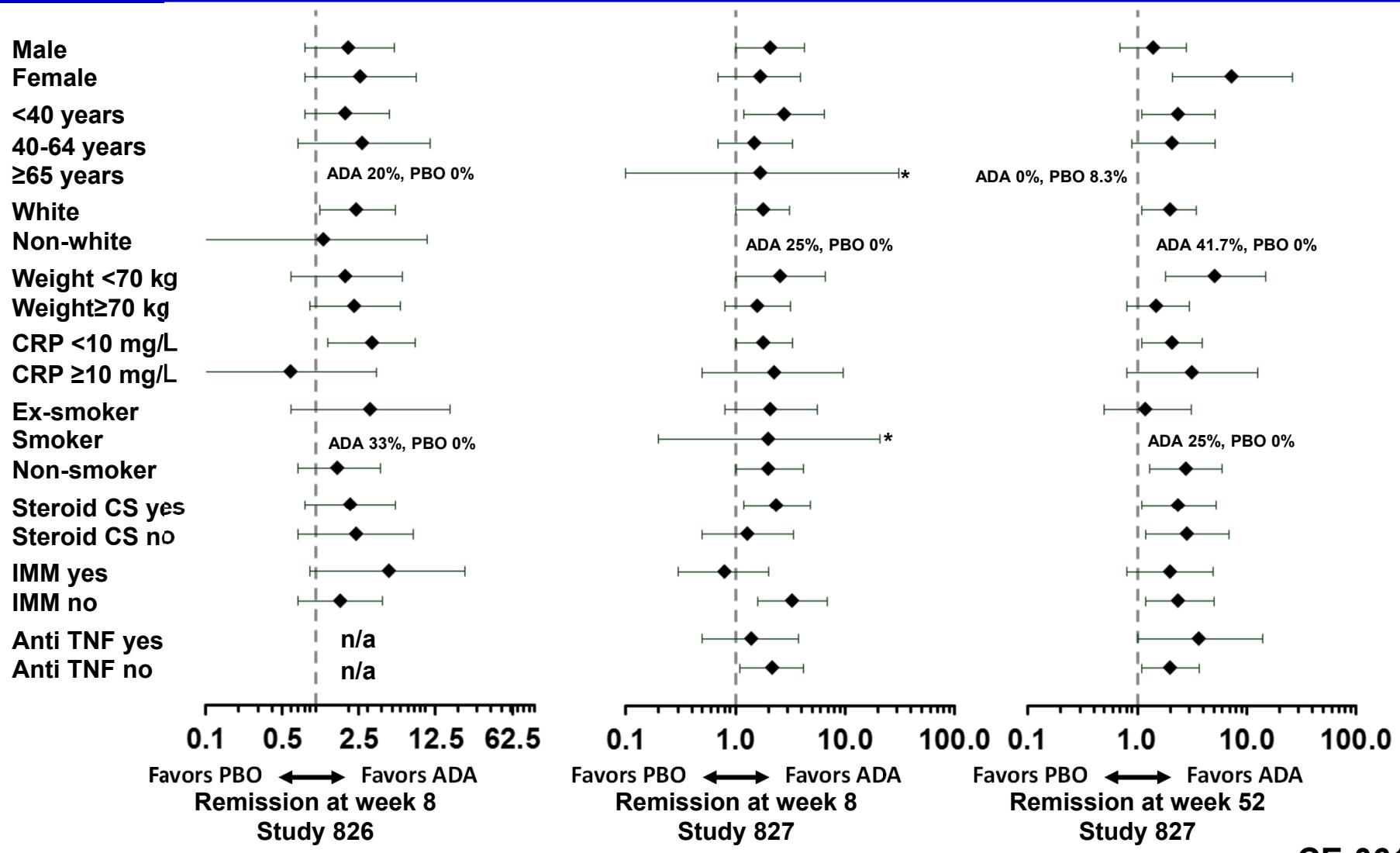
Sustained Efficacy at Weeks 8, 32, and 52

Study 827



CE-060

Odds Ratios for Remission Study 826 and 827



Note: OR adjusted for prior anti-TNF use in 827

* Unadjusted OR < 1

CE-061

Efficacy by Previous Anti-TNF Experience

Study 827

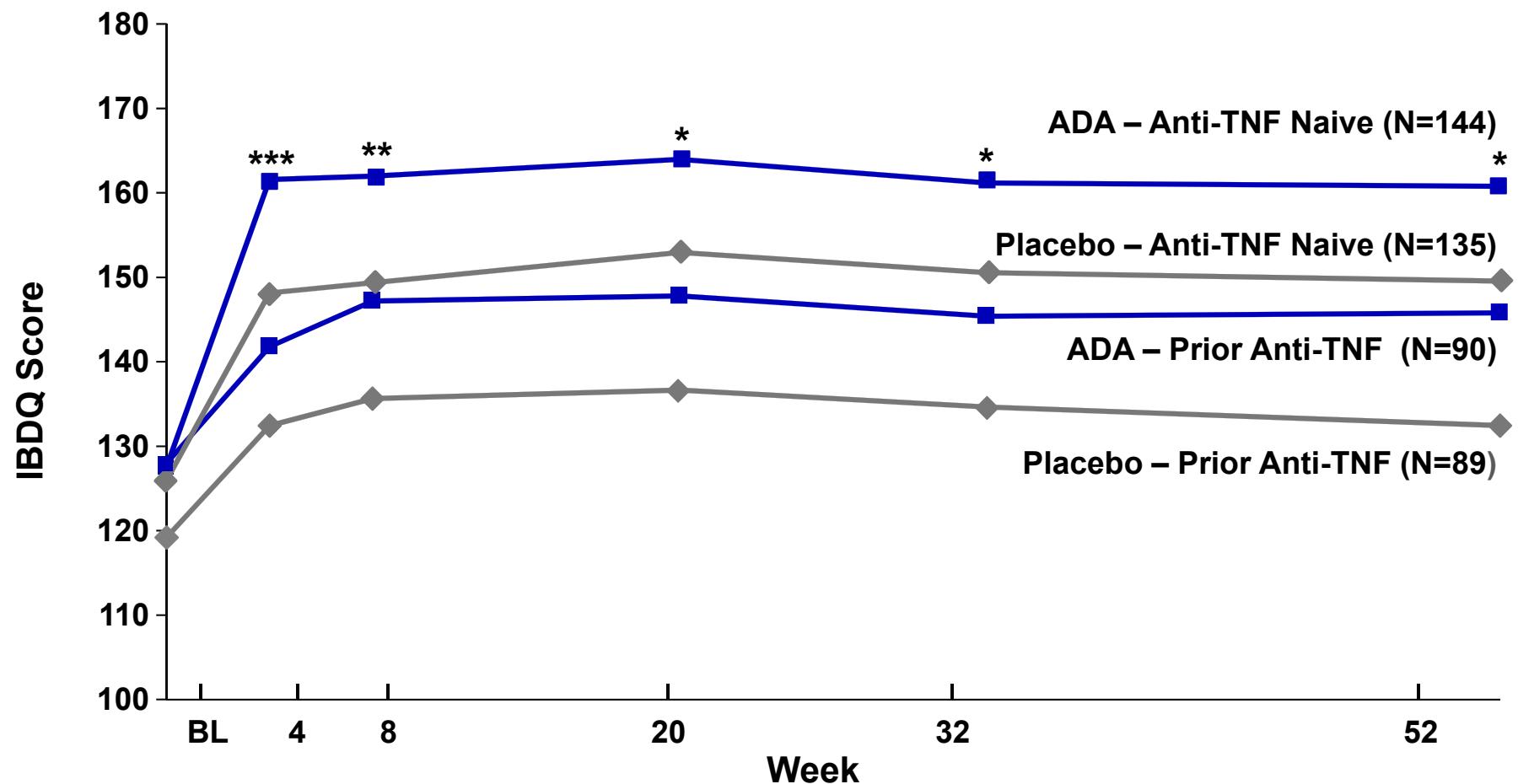
Ranked Endpoints	Anti-TNF Naive			Anti-TNF Experienced		
	Placebo N=145	ADA 160/80 N=150	%Δ	Placebo N=101	ADA 160/80 N=98	%Δ
Remission at Week 8	11.0%	21.3%	10.3	6.9%	9.2%	2.3
Remission at Week 52	12.4%	22.0%	9.6	3.0%	10.2%	7.2
Response at Week 8	38.6%	59.3%	20.7	28.7%	36.7%	8.0
Response at Week 52	24.1%	36.7%	12.5	9.9%	20.4%	10.5
Mucosal healing at Week 8	35.2%	49.3%	14.2	26.7%	28.6%	1.8
Mucosal healing at Week 52	19.3%	31.3%	12.0	9.9%	15.3%	5.4

ITT analysis set

CE-062

Mean IBDQ Scores Over Time By Anti-TNF Experience

Study 827

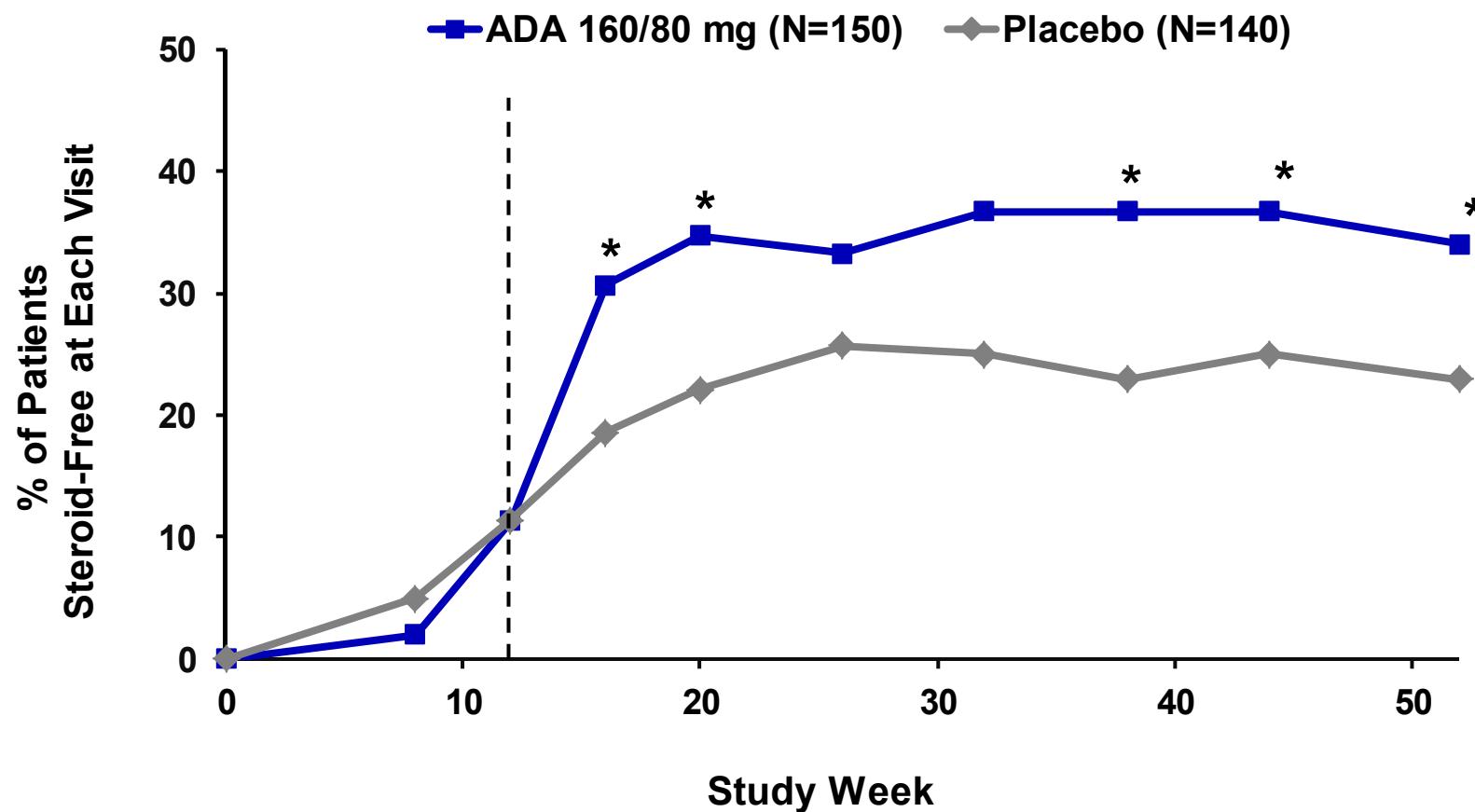


*p<0.05; **p<0.01; ***p<0.001 for ADA 160/80 mg vs placebo; ITT analysis set, LOCF

CE-063

Steroid-Free by Visit

Study 827

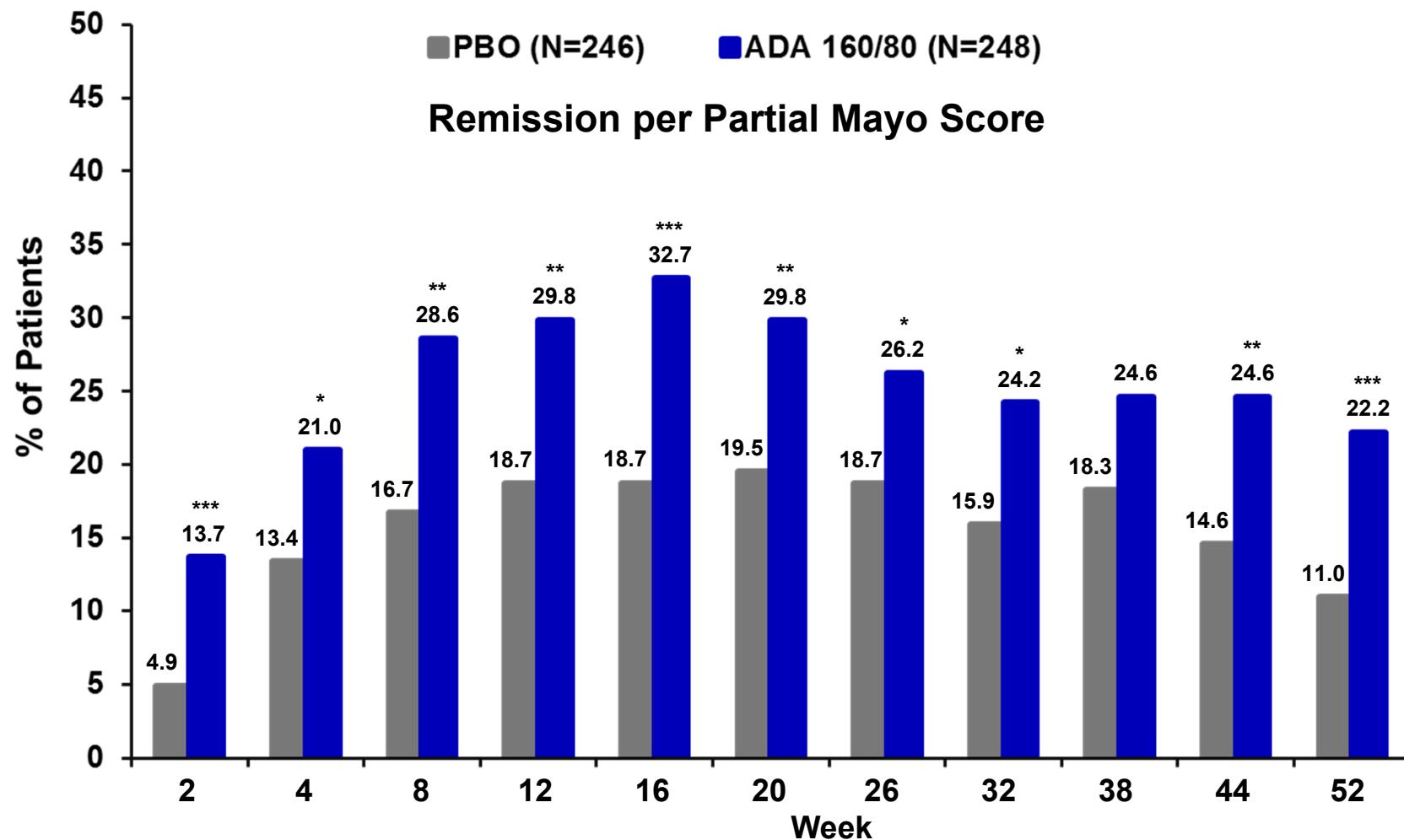


*p<0.05 vs. placebo; patients taking steroids at baseline
P-values based on CMH test with stratification for prior anti-TNF use

CE-064

Remission Over Time

Study 827



*p<0.05, **p<0.01, ***p<0.001 for ADA vs placebo (CMH test with stratification for prior anti-TNF use)
ITT analysis set, NRI for missing/OL data

Efficacy Summary

- **Adalimumab is effective in ulcerative colitis**
 - Established by two positive Phase 3 clinical trials
- **Primary efficacy results at Week 8 and Week 52 are robust**
- **Results are consistent across data sets, endpoints, and subgroups**
 - Effect sizes were greater in anti-TNF naïve patients
- **Efficacy over time consistently favors adalimumab treatment over placebo**

Agenda

- Disease activity measurements
- Study population
- Study designs
- Endpoint descriptions
- Study patients
- Primary and secondary endpoints
- Supportive analyses
- **Exposure/response analyses**

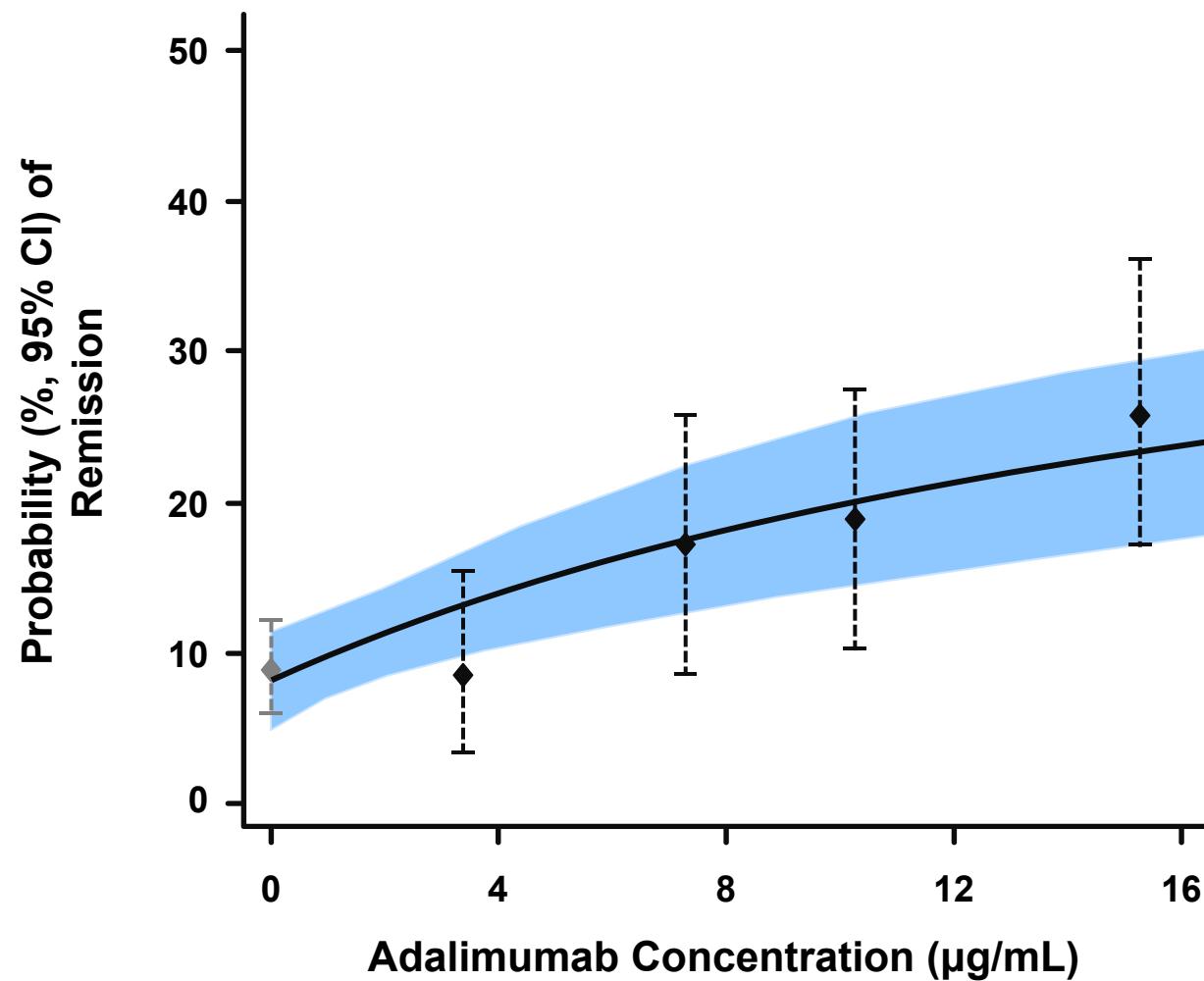
Dose Rationale

- Pharmacokinetic modeling and simulation were performed based on data from Crohn's disease
- Overall efficacy was observed to plateau at maintenance trough exposures of 4 to 8 µg/mL for other adalimumab indications, including Crohn's disease
 - 40 mg eow estimated to provide steady state trough concentrations of 4 to 8 µg/mL in ulcerative colitis patients
- Induction dose of 160/80 mg at Week 0 and 2 would generate adalimumab serum levels higher than what would be expected during maintenance therapy with 40 mg eow

Adalimumab Trough Serum Concentrations Study 827

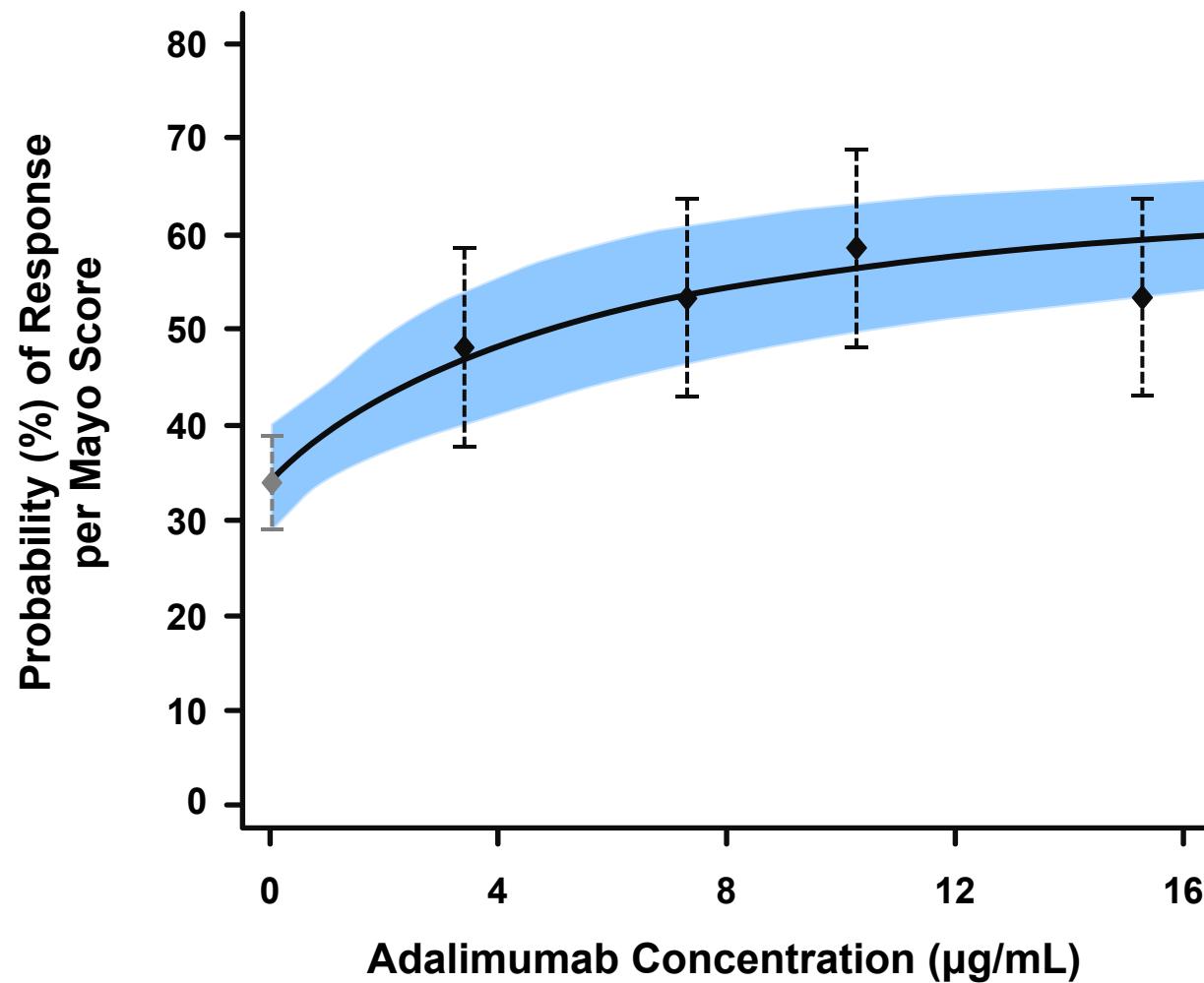
Adalimumab concentration ($\mu\text{g/mL}$) mean \pm SD			
	Week 4	Week 8	Week 52
160/80 mg	11.7 ± 5.5 (N=224)	n/a	n/a
40 mg eow	n/a	8.7 ± 4.8 (N=215)	8.0 ± 6.1 (N=101)
40 mg ew	n/a	n/a	15 ± 8.7 (N=36)

Adalimumab Exposure-Remission Relationship at Week 8



CE-070

Adalimumab Exposure-Response Relationship at Week 8



CE-071

Exposure-Response Summary

- **Exposure-efficacy relationships demonstrate clear biological activity**
- **Efficacy approached plateau at the upper range of observed exposures**
- **It is possible that a higher dose could provide greater efficacy in some patients**
- **Studied dose is appropriate and has a favorable benefit/risk profile**

Safety

Andrea E Best DO, MPH

Senior Medical Director
Immunology Product Safety
Abbott Laboratories Inc.

Extensive Safety Experience

- UC clinical studies: 1,010 patients received at least one dose of adalimumab comprising 2,007 patient-years
- Controlled Crohn's disease trials and registry:
 - Adult Crohn's clinical studies: 1,594 patients
 - Crohn's long term registry: 5,061 patients
- Over 52,000 patient-years across all clinical studies
- Approximately 2 million patient-years of post-marketing experience
- Well characterized safety profile described in labeling

Ulcerative Colitis Safety Comprises 2 Data Sets

Double-Blind Placebo-Controlled Study 826 (0-8 Weeks) and Study 827 (0-52 Weeks)

Adalimumab 160/80 N=480

Adalimumab 80/40 N=130

Placebo N=483

Double-Blind Placebo-Controlled Analysis Set N=1,093

Received open-label or were originally randomized to ADA

Never received ADA N=83

Received Any Adalimumab Study 826, Study 827 or Study 223

N=480

N=130

N=400

All Adalimumab Analysis Set (All ADA) N=1,010

Safety Methods

- For those patients discontinuing the trial during the double-blind period, AE's were collected for 70 days after last dose of ADA or placebo and included in DB safety data set
- For those patients switching to open-label ADA, AE's are included in the all ADA group at or after first dose of OL ADA until 70 days after last dose of ADA. These events are not included as part of the DB safety data set

Immunosuppressive Therapy at Baseline Placebo Controlled Dataset

- The majority of patients in all treatment groups were on immunosuppressive agents at the time of study entry

Placebo Controlled Dataset[†]

	Placebo N=483	ADA 80/40 N=130	ADA 160/80 N=480
Immunomodulatory agents n (%)	177 (36.6)	54 (41.5)	187 (39.0)
Oral corticosteroid n (%)	285 (59.0)	74 (56.9)	287 (59.8)
IMM and/or oral corticosteroid* n (%)	366 (75.8)	100 (76.9)	378 (78.8)

[†] Studies 826 and 827

*IMM = Immunomodulatory Agent and includes AZA, 6-MP or MTX

Week 0-8 Safety Results

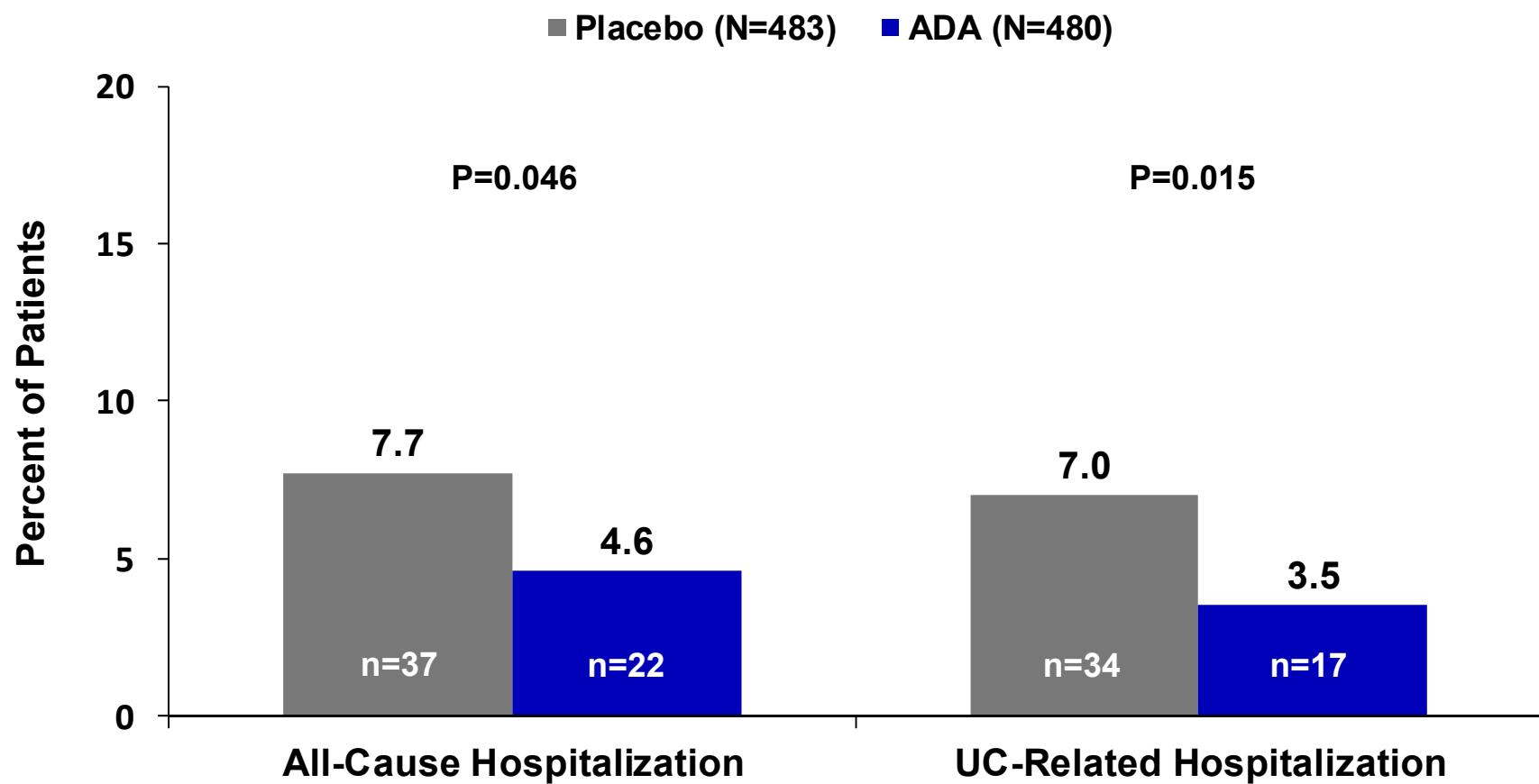
Placebo Controlled Dataset

Patients with:	Placebo N=483 n (%)	ADA 80/40 N=130 n (%)	ADA 160/80 N=480 n (%)
Adverse Events	281 (58.2)	70 (53.8)	267 (55.6)
Discontinuation due to AEs	32 (6.6)	8 (6.2)	24 (5.0)
SAEs	40 (8.3)	5 (3.8)	25 (5.2)
Serious Infections	7 (1.4)	2 (1.5)	3 (0.6)
Any Malignancy	2 (0.4)	0	1 (0.2)
Deaths	0	0	0

Week 0-52 Safety Results Placebo Controlled Dataset

Patients with:	Placebo N=483 PYs=152.9 n (%)	ADA 160/80 N=480 PYs=179.0 n (%)
Adverse Events	327 (67.7)	326 (67.9)
Discontinuation due to AEs	46 (9.5)	36 (7.5)
SAEs	49 (10.1)	40 (8.3)
Serious Infections	8 (1.7)	4 (0.8)
Any Malignancy	2 (0.4)	2 (0.4)
Deaths	0	0

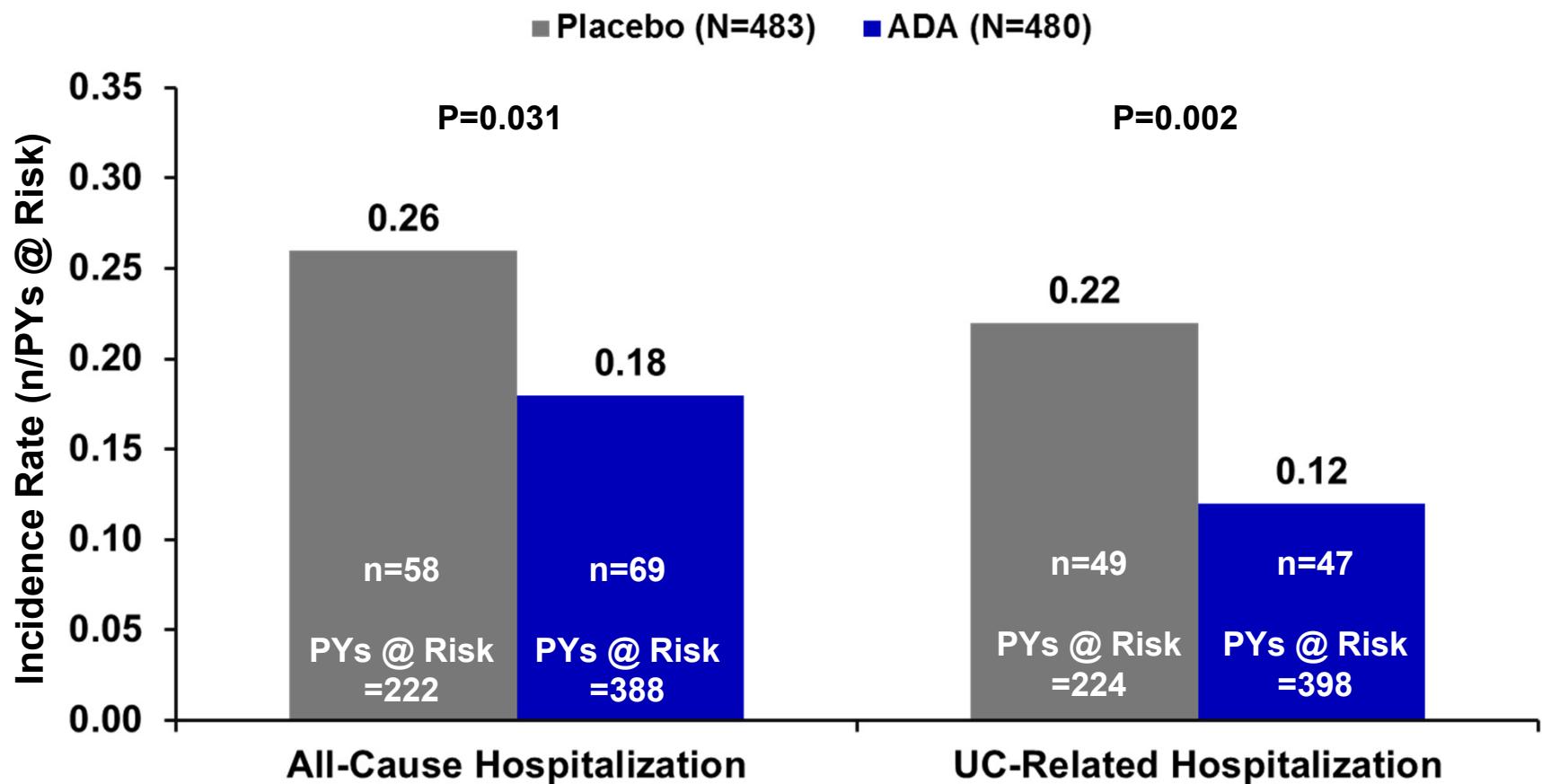
Hospitalization Weeks 0-8 Placebo Controlled Dataset



Statistics: ADA compared with placebo using Chi-square

CS-080

Hospitalization Weeks 0-52 Placebo Controlled Dataset



PYs @ Risk: patient-years at risk
Statistics: p-value based on Z score

Long-Term Safety Data Consistent with Controlled Trials

	Placebo Controlled Dataset (0-52 wks)	Open Label and Controlled Dataset	
	Placebo N=483 PYs=152.9 Events (E/100 PYs)	ADA 160/80 N=480 PYs=179.0 Events (E/100 PYs)	All ADA N=1010 PYs=2007.4 Events (E/100 PYs)
Discontinuations due to AEs	62 (40.6)	39 (21.8)	235 (11.7)
SAEs	69 (45.1)	54 (30.2)	374 (18.6)
Serious Infections	10 (6.5)	4 (2.2)	68 (3.4)
Any Malignancy	2 (1.3)	2 (1.1)	21 (1.1)
Deaths	0	0	2 (0.1)*

* In addition 2 post-treatment deaths

Serious Adverse Events (≥ 5 Events) Placebo Controlled and All ADA

	Placebo Controlled Dataset (0-52 wks)		Open Label and Controlled Analysis
	Placebo N=483 PYs=152.9 Events (E/100 PYs)	ADA 160/80 N=480 PYs=179.0 Events (E/100 PYs)	All ADA N=1010 PYs=2007.4 Events (E/100 PYs)
Any SAE	69 (45.1)	54 (30.2)	374 (18.6)
Colitis ulcerative	34 (22.2)	21 (11.7)	103 (5.1)
Anemia	2 (1.3)	2 (1.1)	12 (0.6)
Appendicitis	0	1 (0.6)	8 (0.4)
Osteoarthritis	0	0	8 (0.4)
Pneumonia	2 (1.3)	0	7 (0.4)
Anal abscess	1 (0.2)	1 (0.2)	5 (0.3)
Inguinal hernia	0	0	5 (0.3)
DVT	1 (0.7)	2 (1.1)	5 (0.3)

Injection Site Reactions in Ulcerative Colitis Trials

Weeks 0-52 and All ADA

	Placebo N = 483 PYs = 152.86	ADA 160/80 N = 480 PYs = 178.95	All ADA N = 1010 PYs = 2007.4
Preferred Term	n (%)	n (%)	n (%)
Injection site reaction	17 (3.5)	44 (9.2)	108 (10.7)
Injection site erythema	3 (0.6)	16 (3.3)	33 (3.3)
Injection site pain	12 (2.5)	12 (2.5)	19 (1.9)
Injection site reaction	2 (0.4)	12 (2.5)	37 (3.7)
Injection site pruritus	2 (0.4)	9 (1.9)	20 (2.0)
Injection site swelling/edema	0	5 (1.0)	13 (1.3)
Injection site hematoma	0	4 (0.8)	12 (1.2)
Injection site rash/eczema	1 (0.2)	3 (0.6)	6 (0.6)
Injection site induration/warmth	0	2 (0.4)	8 (0.8)
Injection site mass/nodule	0	1 (0.2)	2 (0.2)
Injection site hypersensitivity	0	0	3 (0.3)
Injection site cellulitis	0	0	1 (<0.1)
Injection site abscess	0	0	1 (<0.1)

Ulcerative Colitis Registry

- Post-approval commitment in the EU and proposed as post-marketing commitment for US
- A global multicenter, non-interventional registry of adult patients with moderately to severely active UC treated in a routine clinical setting
- ~5,500 patients prescribed adalimumab and ~2,750 patients prescribed 6-MP or AZA without adalimumab or another biologic will be followed long term

Summary of Ulcerative Colitis Safety

- **Safety profile for adalimumab was comparable to placebo during controlled studies**
- **No new safety signals identified during the open-label ulcerative colitis studies**
- **Safety experience in ulcerative colitis is consistent with the established safety profile of adalimumab**
- **Ulcerative colitis registry will provide additional long-term safety information**

Benefit/Risk Assessment

Roopal Thakkar, MD

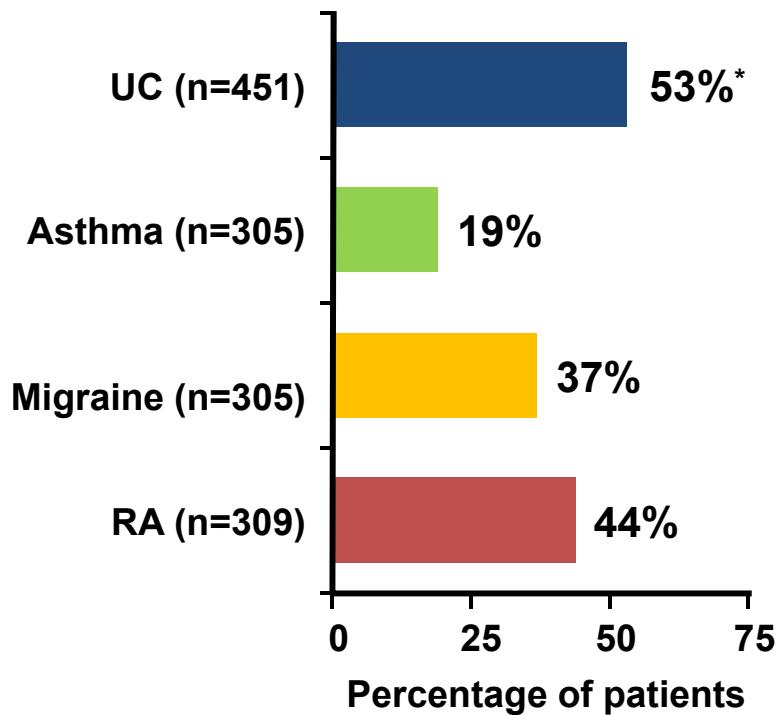
Project Director, Immunology
Abbott Laboratories Inc.

Benefit/Risk Assessment Considerations

- **Disease state/severity**
- **Available therapies and limitations**
- **Efficacy**
- **Safety**
- **Supportive combined (efficacy and safety) analyses**
- **Enhancement of benefit/risk profile**

Disease State/Severity

Proportion of patients who feel their condition was controlling their lives¹



- Patients with UC have a poor quality of life
- 34% of patients in the US with moderate to severe UC hospitalized per year¹
- Many patients will require surgery

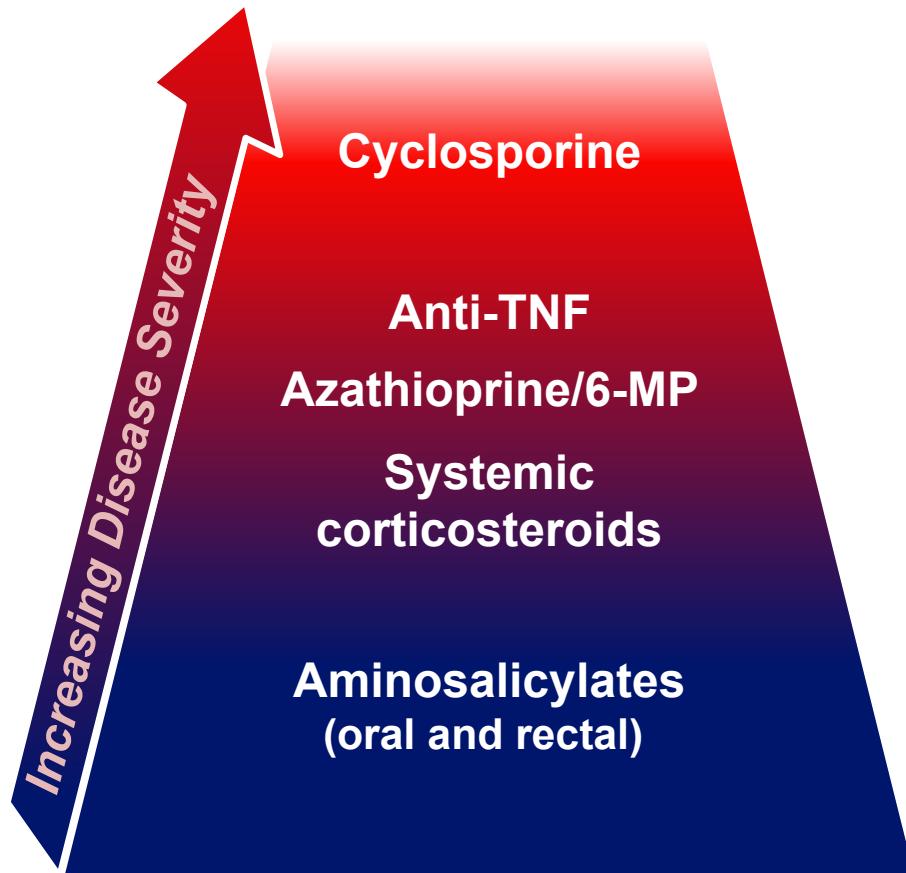
*p<0.05 vs other chronic conditions

1. Rubin DT et al. *Dig Dis Sci*. 2010; 2. Cohen RD et al. Submitted to ACG 2012

Disease Burden Was High in the Adalimumab UC Trials

- These patients had considerable disease burden and few treatment options (mean Mayo score ~9)
- All patients had inadequate response to conventional therapy (steroids and IMMs)
- 40% of patients had already failed anti-TNF therapy
 - About one-third of these patients had already dose-escalated on this therapy

Available Therapies are Limited

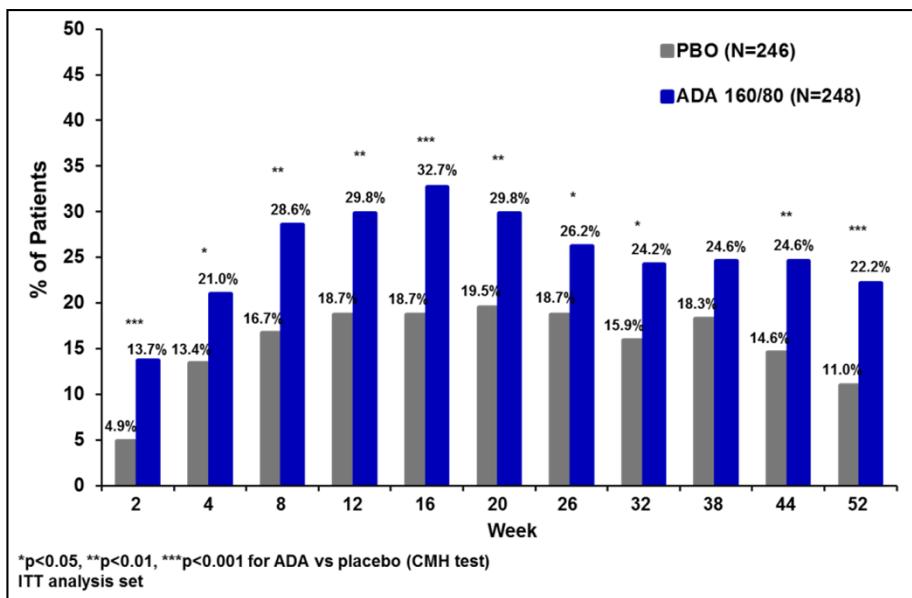
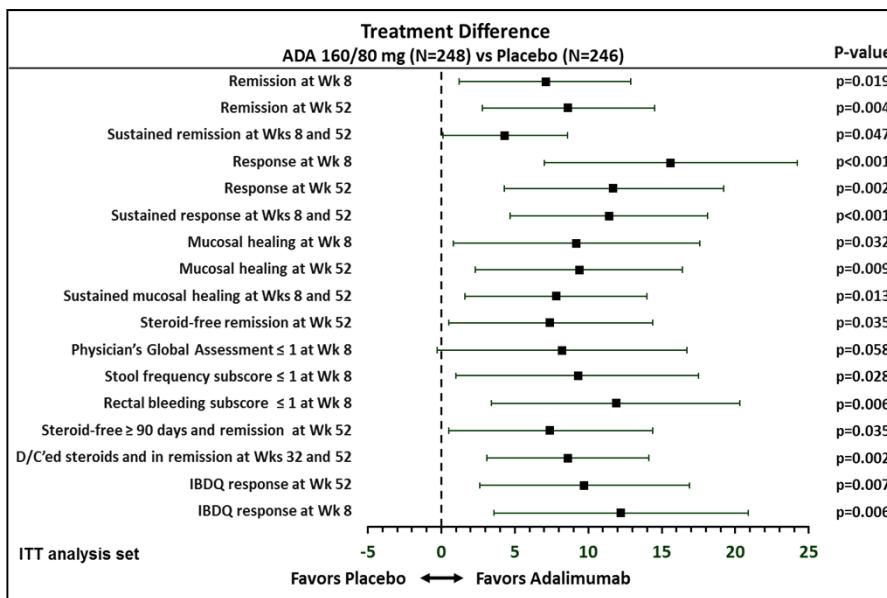


- Steroids are not a viable long-term option
- IMM data are limited and they are not FDA-approved
- Only one anti-TNF agent is approved

Adapted from Hanauer SB. *Aliment Pharmacol Ther.* 2008.

Efficacy

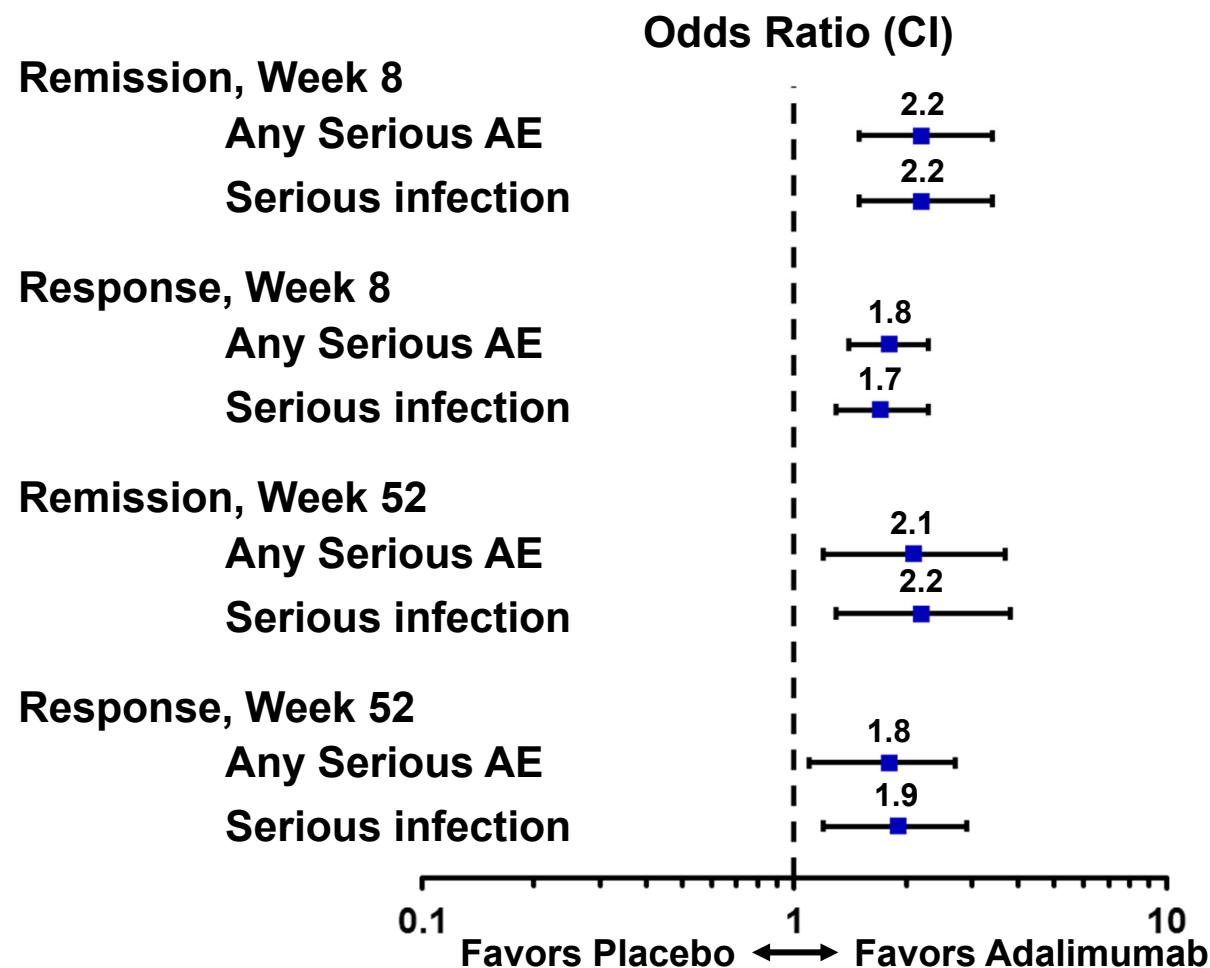
- Both trials achieved their primary endpoints
- Treatment effects consistently favored adalimumab across endpoints, time points and were durable



Benefit/Risk Safety

Weeks 0-52				
Preferred term	Placebo N=483 PYs=152.9		Adalimumab 160/80 N=480 PYs=179.0	
	N (%)	Events (E/100 PY)	N (%)	Events (E/100 PY)
Any SAE	49 (10.1)	69 (45.14)	40 (8.3)	54 (30.18)
Serious infection	8 (1.7)	10 (6.54)	4 (0.8)	4 (2.24)
Any malignancy	2 (0.4)	2 (1.31)	2 (0.4)	2 (1.12)

Efficacy Without Experiencing an Adverse Event Studies 826/827



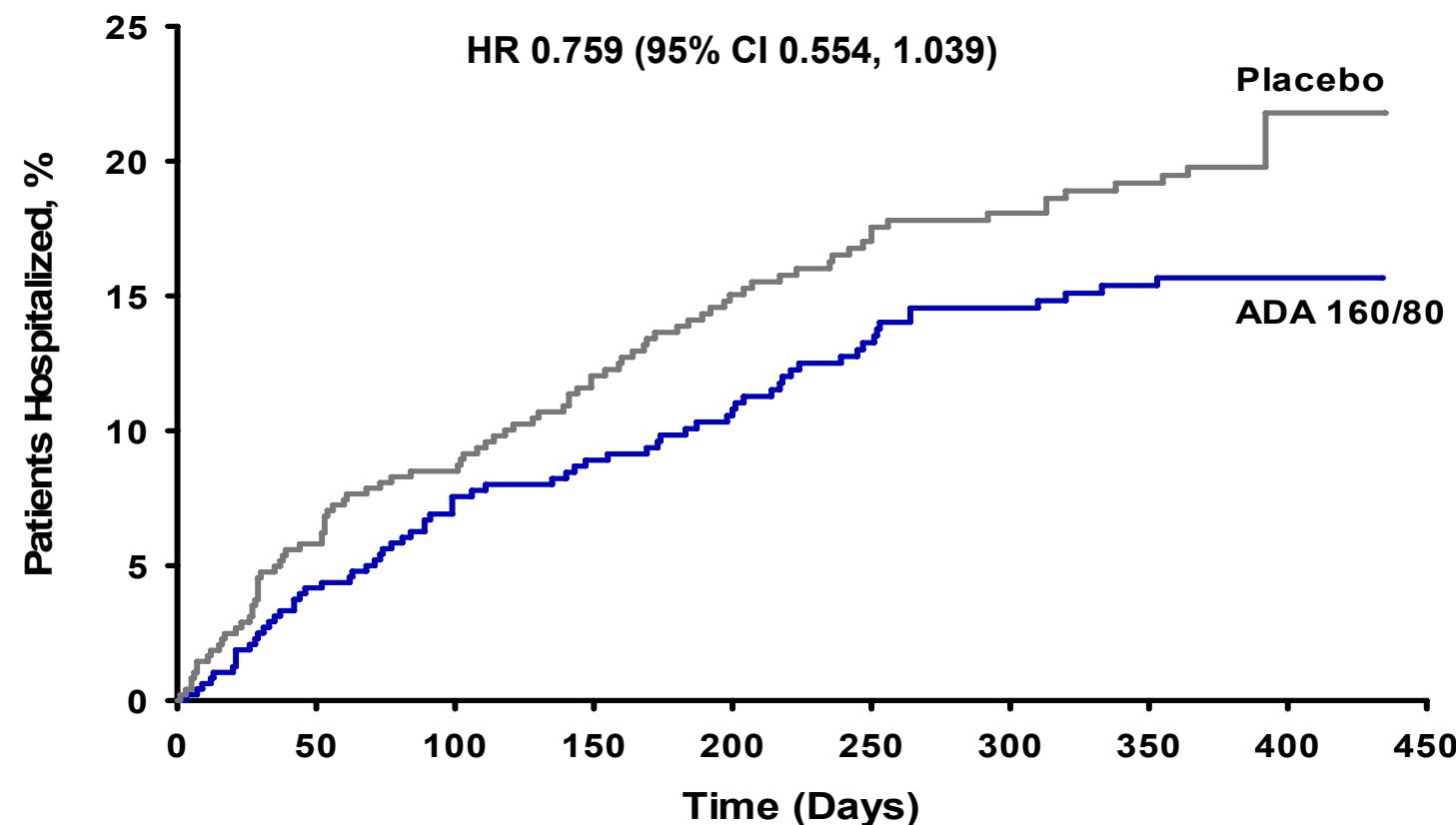
Based on Boada, et al, PLoS ONE 3(10): e3580

CB-094

All-Cause Hospitalization Represents A Combined Measure of Benefit/Risk

- Treatment benefits may reduce disease-related hospitalization
- Treatment risks may result in hospitalizations due to adverse events
- All-cause hospitalization considers both benefits and risks

As-Randomized All-Cause Hospitalization Weeks 0-52 Studies 826/827 ITT Safety Data Set



At risk:

Placebo	483	455	420	389	358	321	304	284	34	0
ADA 160/80	480	460	417	399	373	342	309	298	41	0

Log-Rank p=0.084

Cox proportional hazards model p=0.085

CB-096

US Labeling for Crohn's Disease

“Among patients who were not in response by Week 12, therapy continued beyond 12 weeks did not result in significantly more responses.”

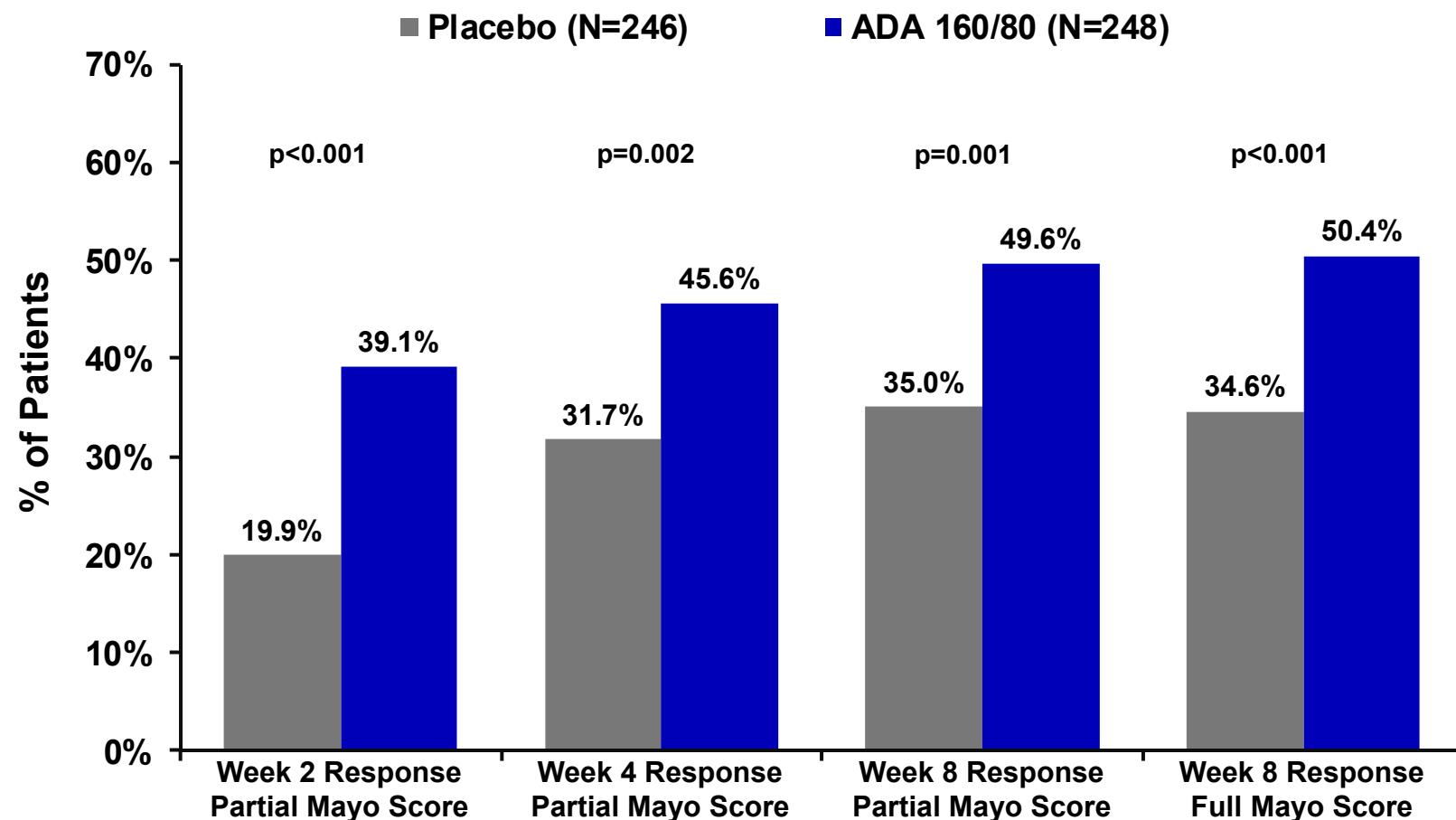
- Adalimumab US labeling
(Clinical Studies, Crohn's Disease Section 14.5)

EU Labeling for Ulcerative Colitis

- **Current adalimumab European label language regarding use in ulcerative colitis:**
 - Available data suggest that clinical response is usually achieved within 2-8 weeks of treatment. HUMIRA therapy should not be continued in patients failing to respond within this time period.
- **These recommendations are based on evaluation of early response during the induction period in the UC maintenance trial**

Response Rates Through Week 8

Study 827

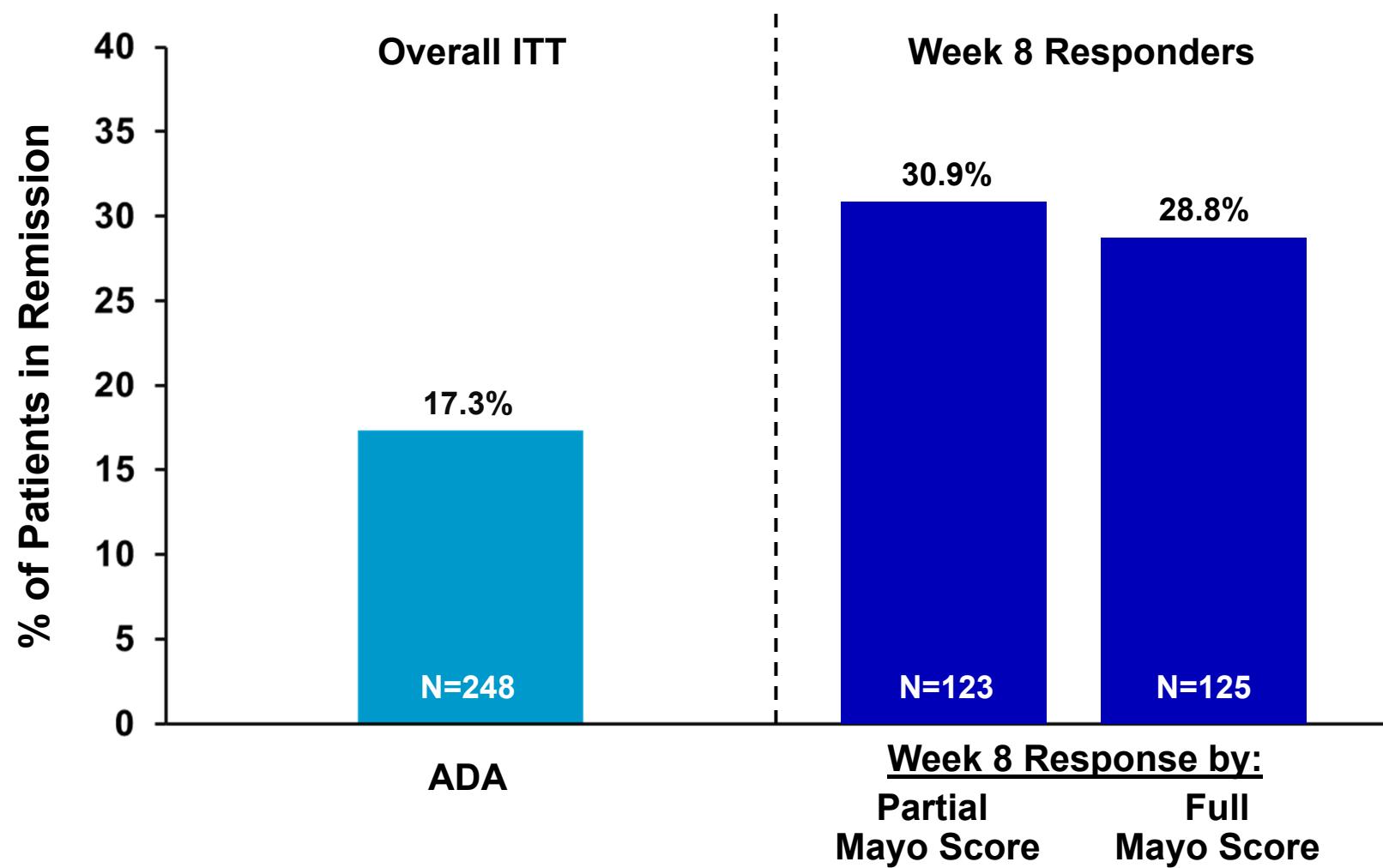


ITT analysis set, pre-specified per statistical analysis plan

CB-099

Week 52 Remission

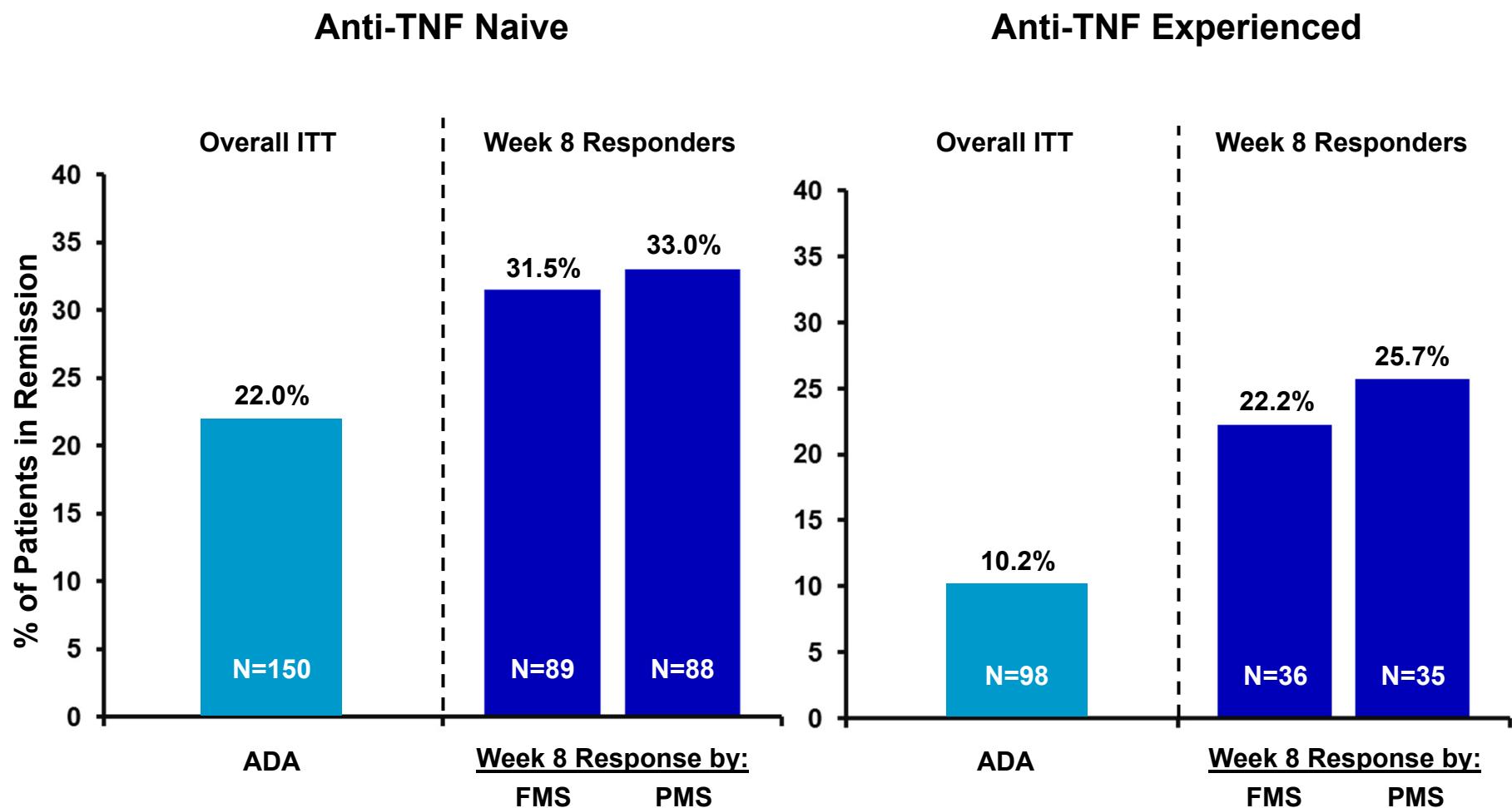
Study 827



CB-100

Week 52 Remission by Anti-TNF Experience

Study 827



Proposed Label Language

HUMIRA should only be continued in patients who have responded during the first 8 weeks of therapy.

Proposed Label Language

For patients who respond and then lose their response, consideration may be given to increasing the dosing frequency of HUMIRA to 40 mg every week.

Summary of Benefit/Risk Assessments

- Patients with moderate to severe UC have substantial disease burden and limited treatment options
- Treatment effects consistently favored adalimumab across endpoints and time points and were durable
- The safety profile is well-characterized and no new safety signals were noted in UC
- Combined assessments of benefit and risk provide further evidence of a favorable profile
- Limiting use to early responders further enhances the benefit/risk profile

Proposed Indication

HUMIRA is indicated for reducing signs and symptoms and achieving clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.

Clinical Perspective

William J. Sandborn, MD

Professor of Clinical Medicine
Chief, Division of Gastroenterology
University of California San Diego School of Medicine

Current Therapy for Ulcerative Colitis

	Induction	Maintenance
Mesalamine	+	+
Steroids	+	-
Azathioprine/6-MP	-	?
Infliximab	+	+?

Design Characteristics for Trials with Biologic Agents in CD and UC

Short-term Induction

CD - Targan/CLASSIC I
UC - Adalimumab 826



Maintenance

CD - ACCENT/PRECISE 2 /CHARM
UC - none



"Induction and Maintenance"

CD - PRECISE 1
UC - Infliximab ACT 1 + 2
Adalimumab 827

- | | | |
|---------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none">• Placebo-controlled induction• Endpoints of response or remission over 4-12 weeks | <ul style="list-style-type: none">• Open label induction• Followed by maintenance with active drug or placebo in responders• Endpoint of response or remission at 6-12 months | <ul style="list-style-type: none">• Double-blind, placebo controlled induction and maintenance, not selected for responders• Co-primary induction and maintenance endpoints (response or remission)• Secondary endpoints of sustained remission or response for induction + maintenance |
|---------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

Why You Shouldn't Compare Across Clinical Trials

	Study 826	Study 827	ACT 1	ACT 2
Parallel group design	✓	✓	✓	✓
Primary endpoint	Remission at wk 8	Remission at wk 8 Remission at wk 52	Response at wk 8	Response at wk 8
Requirement for steroid and/or IMM failure	✓	✓	✓	
Inclusion of anti-TNF failure patients		✓		
Mayo scoring methodology	Worst-rank	Worst-rank	Average	Average
OL escape allowance		✓		
Timing of primary endpoint efficacy assessments	Trough	Trough	2 wks post-infusion	2 wks post-infusion

UC Drug Development Guidance (2006-Present)

- No published guidance specific to ulcerative colitis trial design or endpoints
- Approvals for maintenance therapy not based on trials with re-randomization of responders or remitters
- No guidance on use of remission (versus response) as primary endpoint
- Limited experience with sustained remission as a ranked secondary endpoint

Patients in the 826 and 827 Trials Had Refractory Disease

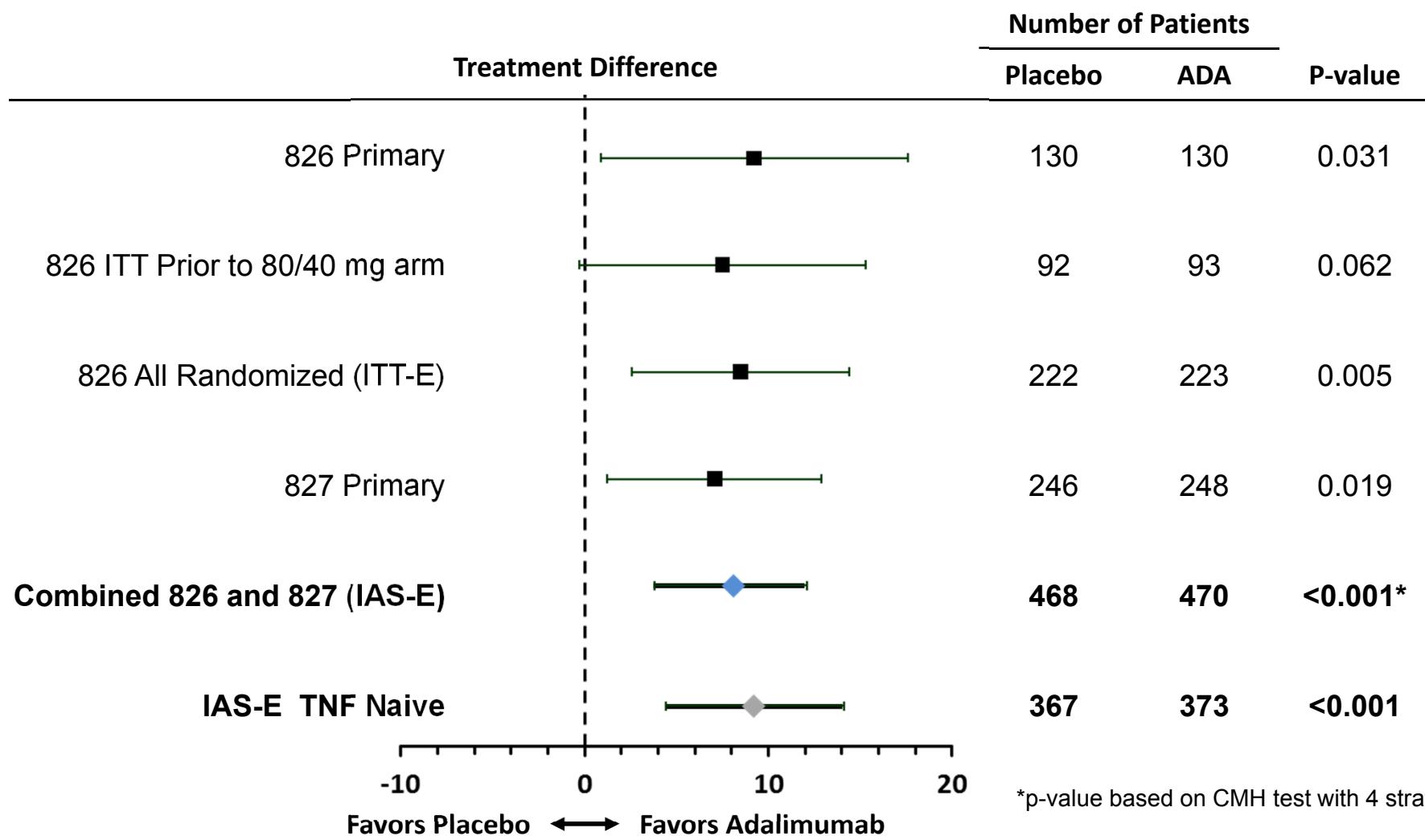
- **Moderately to severely ill at baseline**
 - Mayo score ~9
 - IBDQ score ~125
 - ~50% of patients had pancolitis
- **Immunosuppressive therapy**
 - 75% of study patients had moderate to severe symptoms despite ongoing therapy
- **In Study 827, 40% of patients had failed previous anti-TNF therapy**
 - ~One-third of these patients had dose escalated

Adalimumab Study Results Are Statistically Robust and Clinically Meaningful

- Two positive randomized well-controlled clinical trials in a moderately to severely ill population**
- Benefits were observed across multiple measures of efficacy and across time points**

Remission at Week 8

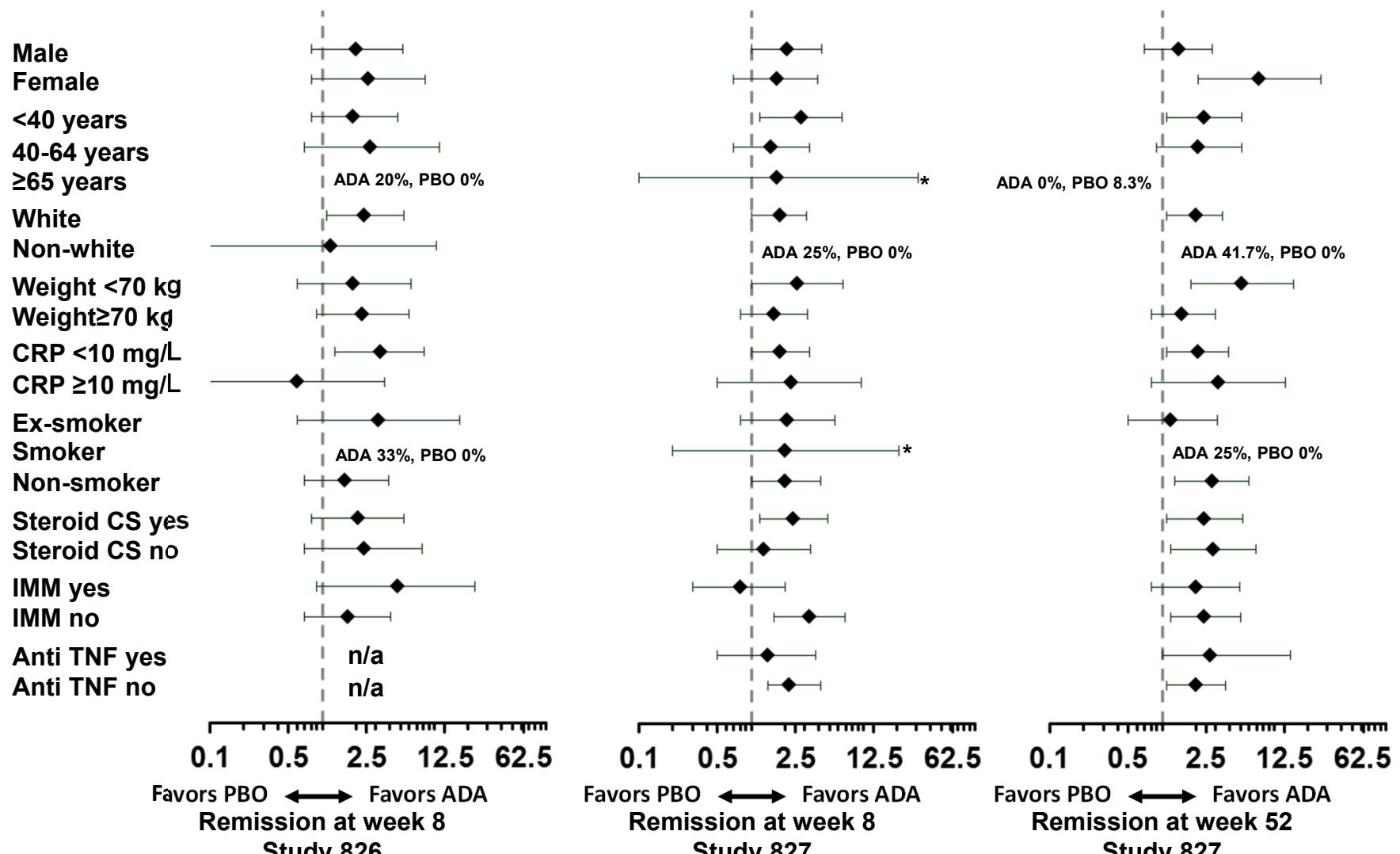
Studies 826/827



*p-value based on CMH test with 4 strata

Odds Ratios for Remission

Study 826 and 827

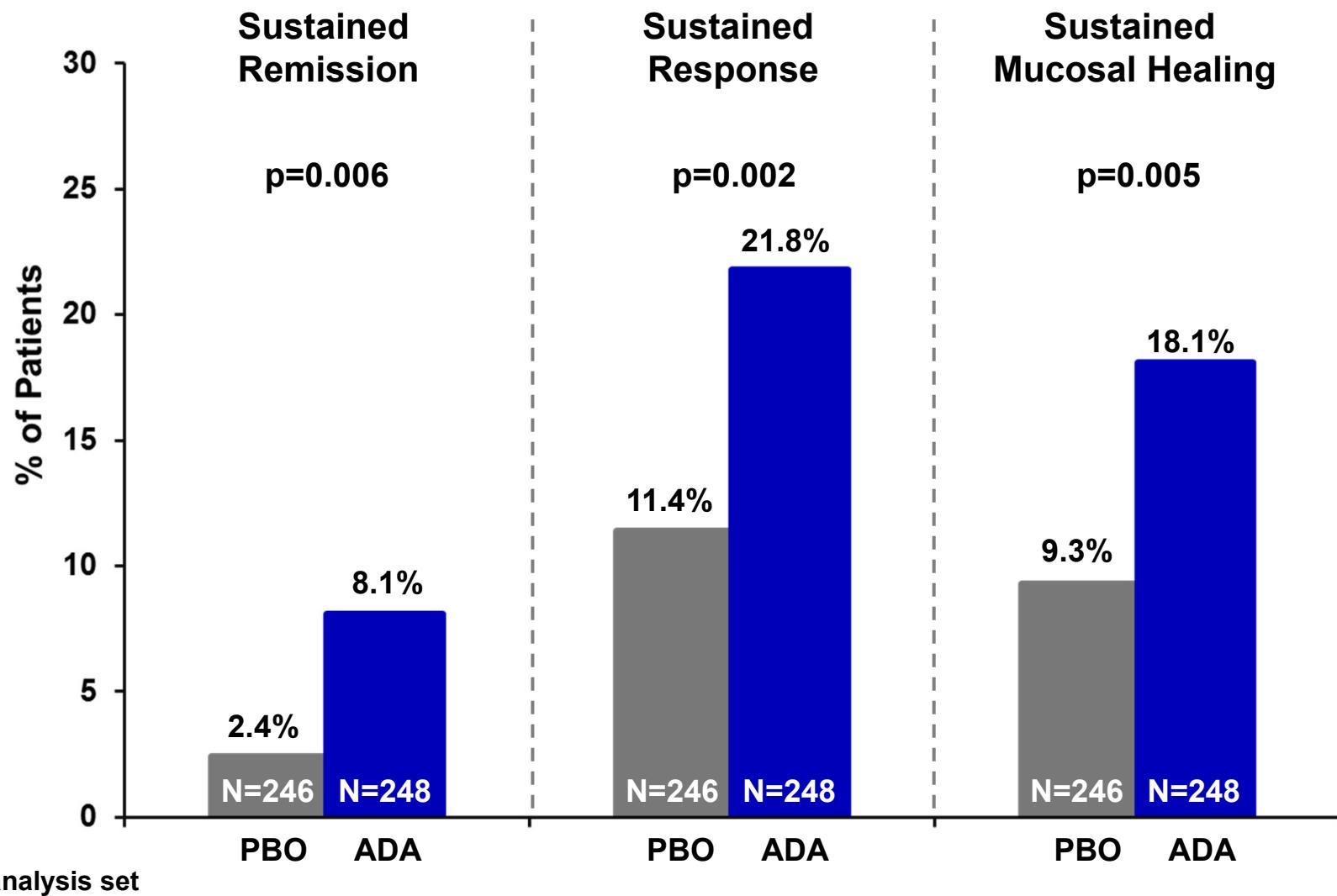


Note: OR adjusted for prior anti-TNF use in 827

* Unadjusted OR < 1

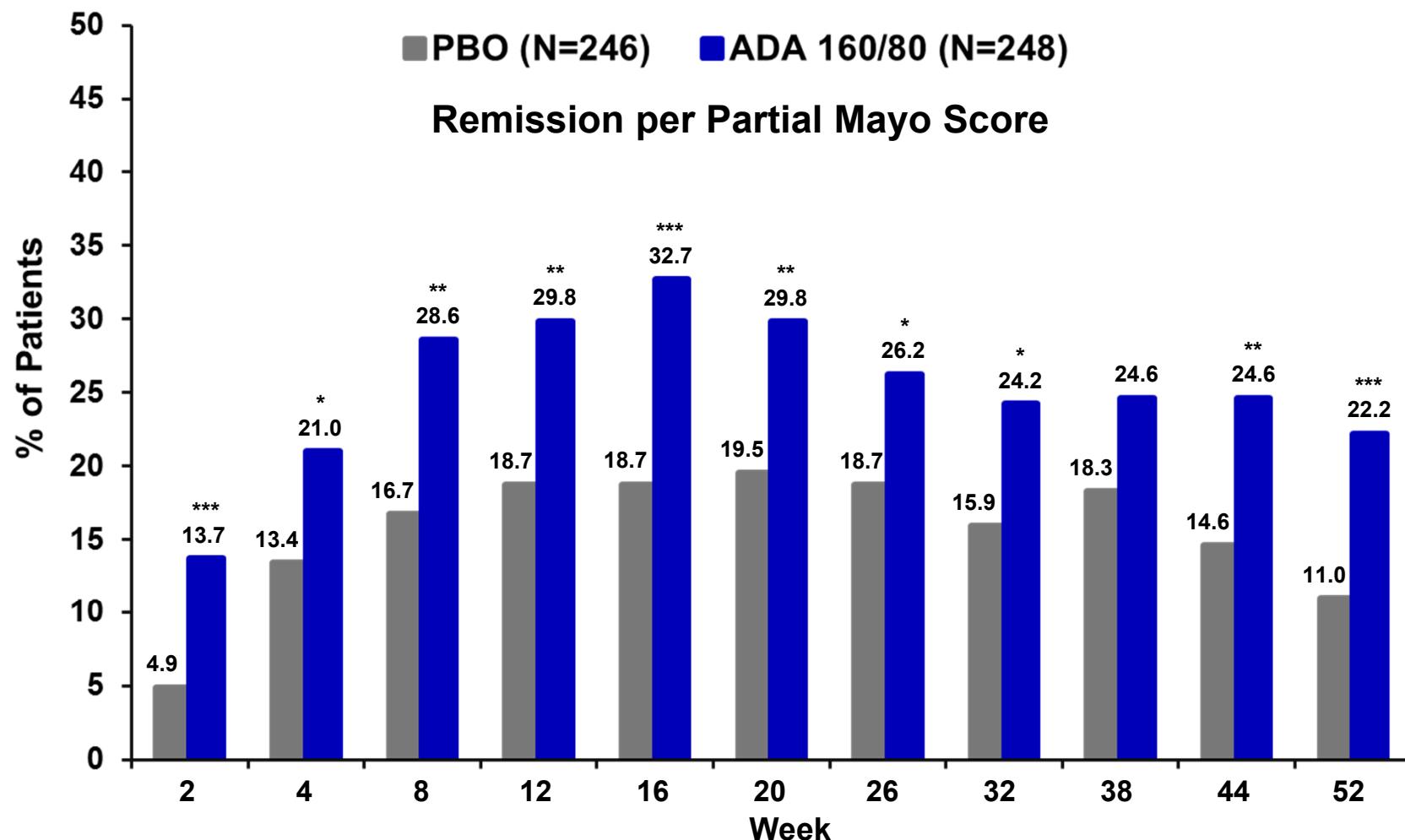
Sustained Efficacy at Weeks 8, 32, and 52

Study 827



Interpretation of Long-Term Data

Study 827



*p<0.05, **p<0.01, ***p<0.001 for ADA vs placebo (CMH test)

ITT analysis set

Adequacy of Studied Dose

- The studied dose is appropriate and is associated with a favorable benefit/risk profile
 - Dose is adequate in Week 8 responders
- Exposure-efficacy relationships demonstrate clear biologic activity
- It is possible that a higher dose could have led to greater efficacy in some patients

Clinical Meaningfulness of Data

- Anti-TNF naive patients versus anti-TNF experienced
- Steroid-sparing
- Quality of life
- Hospitalization
 - Disease-related hospitalization
 - All-cause hospitalization

Which Patients Benefit Most From Adalimumab Therapy?

- **Statistically significant benefit in the ITT population**
 - Larger treatment difference in anti-TNF naive patients
- **Larger treatment benefit in patients responding at Week 8**
 - Response at 8 weeks → 30% remission
 - Consistent across endpoints (mucosal healing, steroid reduction)
 - Including anti-TNF experienced patients
- **Consistent with clinical practice in the US with all approved biologics in Crohn's disease and ulcerative colitis**

Summary

- **Clear need for additional therapies in UC**
- **Adalimumab provides clinically meaningful benefits to patients, especially among Week 8 responders (including infliximab exposed patients)**
- **Safety profile is very well-characterized and manageable**
- **Benefit/risk is clearly favorable, and enhanced by restricting long term treatment to Week 8 responders**
- **Evaluation of early response to determine continued therapy is standard practice**

Conclusion

John Medich, PhD

Divisional Vice President,
Immunology Clinical Development
Abbott Laboratories Inc.

Conclusions

- Many patients with UC experience inadequate response with available therapies and would benefit from additional pharmacologic treatment options
- The benefits of adalimumab outweigh the risks in patients with inadequate response to available therapies
- Benefit/risk is enhanced by limiting continued treatment to patients who respond within the first 8 weeks of therapy
- If approved, only biologic in US for UC that can be self-administered

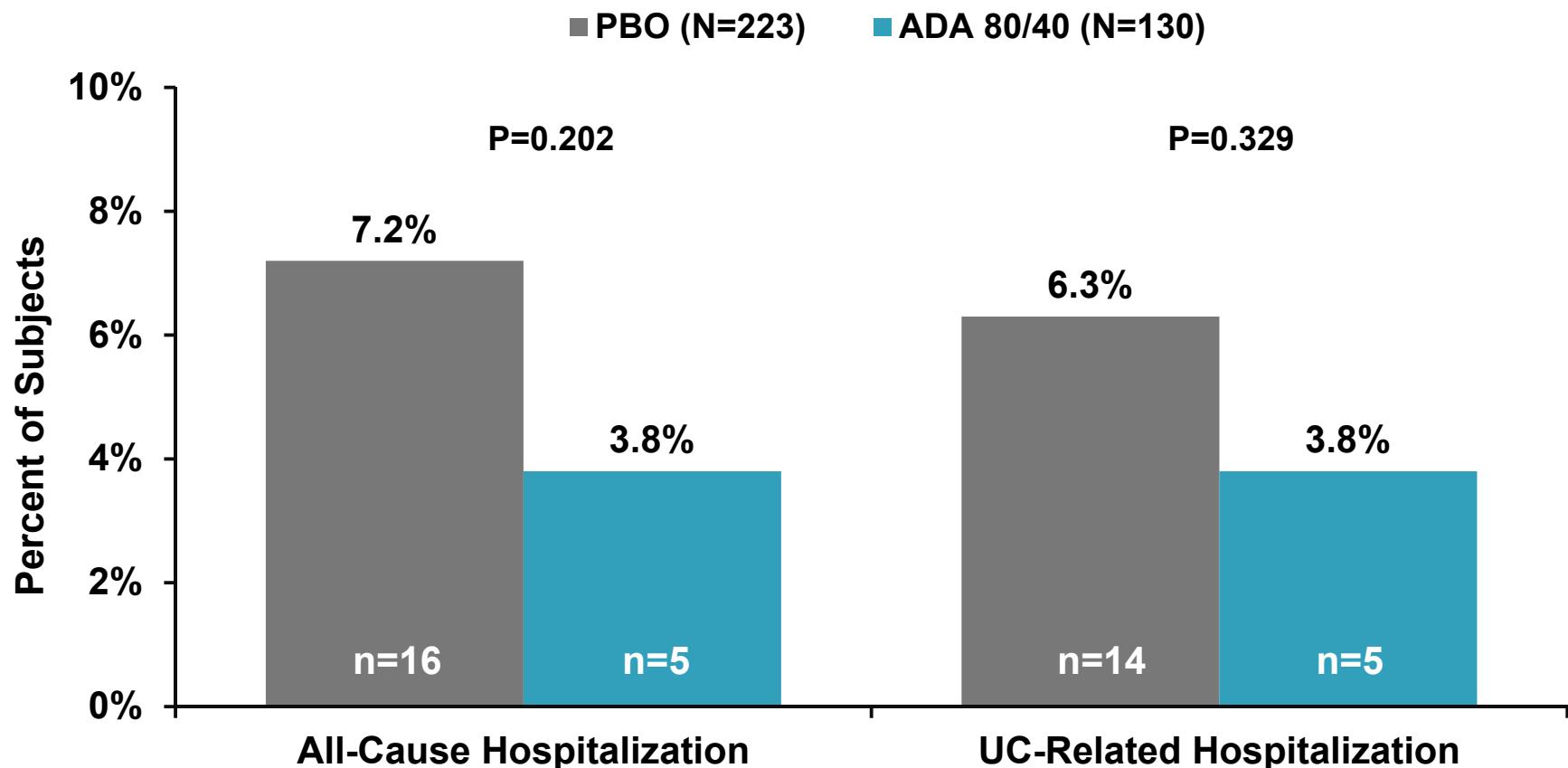
Conclusions

- Adalimumab is proposed for the indication of reducing signs and symptoms, and achieving clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy
 - Treatment should only be continued in patients who have responded during the first 8 weeks of therapy.
 - For patients who respond and then lose their response, consideration may be given to increasing the dosing frequency to 40 mg every week.

Backup Slides Shown

Hospitalizations Subgroup Analyses

Weeks 0-8 Study 826 (ITT-E)



826 Safety Dataset

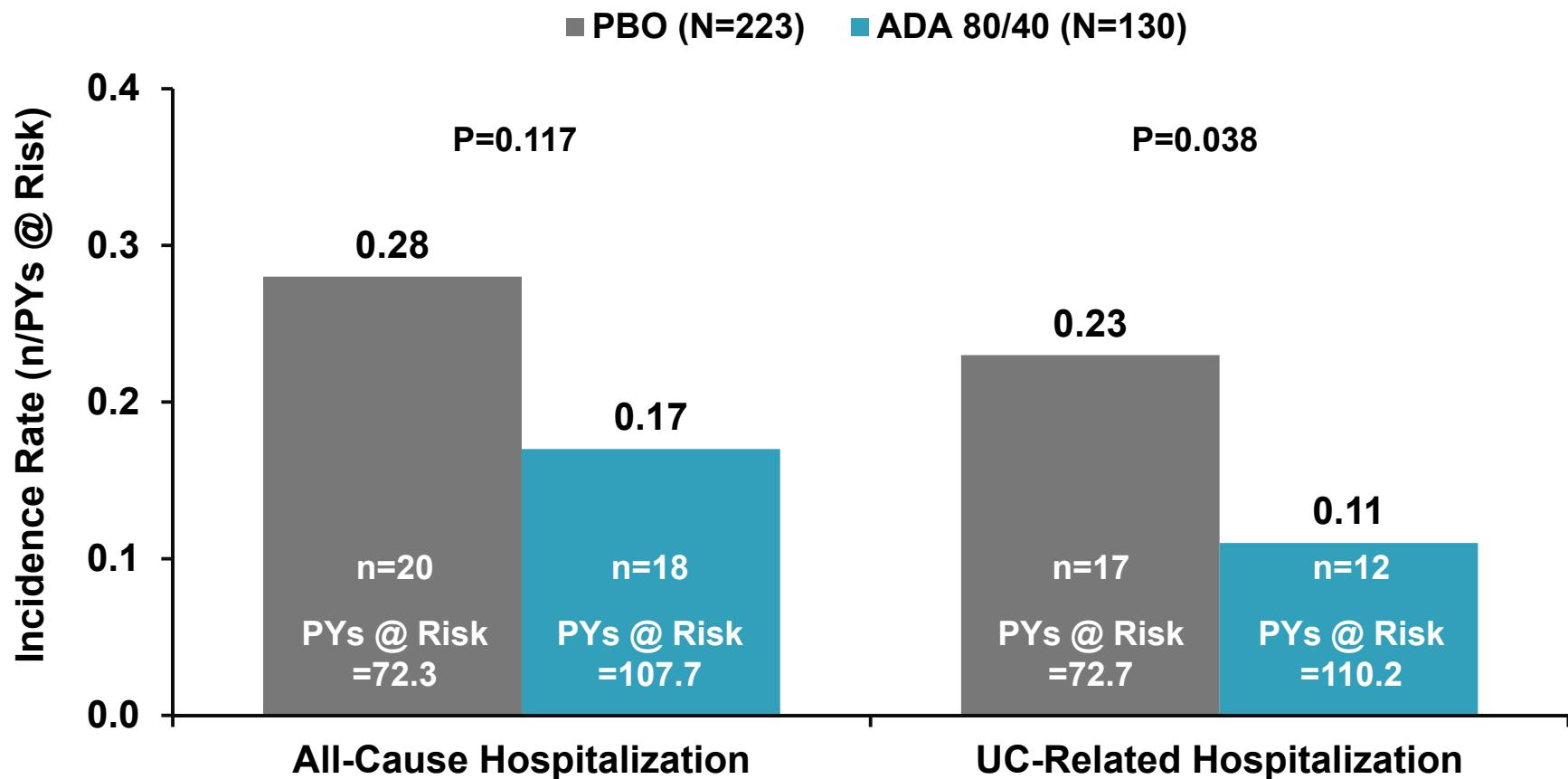
n=number of patients with hospitalization

P-values based on Chi-square test

HP-073S

Hospitalizations Subgroup Analyses

Weeks 0-52 Study 826 (ITT-E)



826 Safety Dataset

PYs @ Risk=patients years at risk; n=number of patients with hospitalization

P-values based on Z score normal approximation

HP-076S

UC-related Hospitalizations

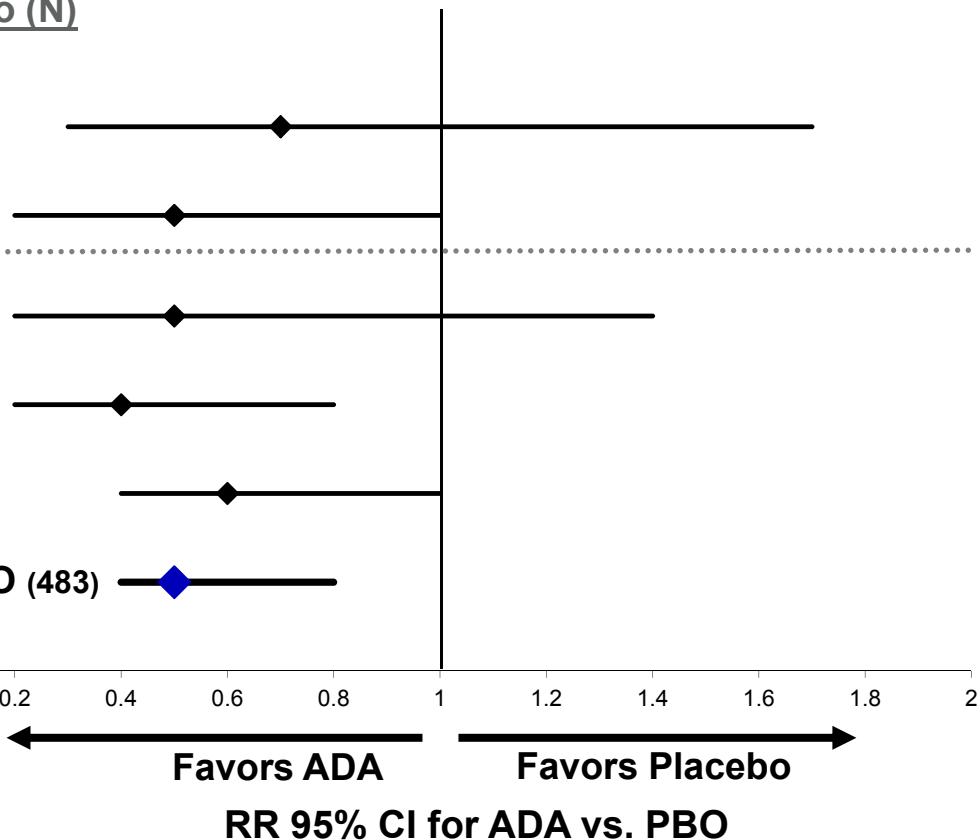
Subgroup Analyses

Weeks 0-52 Studies 826 and 827

UC-related Hospitalizations Relative Risk (Weeks 0-52)

Subpopulations: Adalimumab (N) vs. Placebo (N)

826 ITT-A3, 80/40 ADA (130) vs. PBO (130)



RR=relative risk

HP-070S

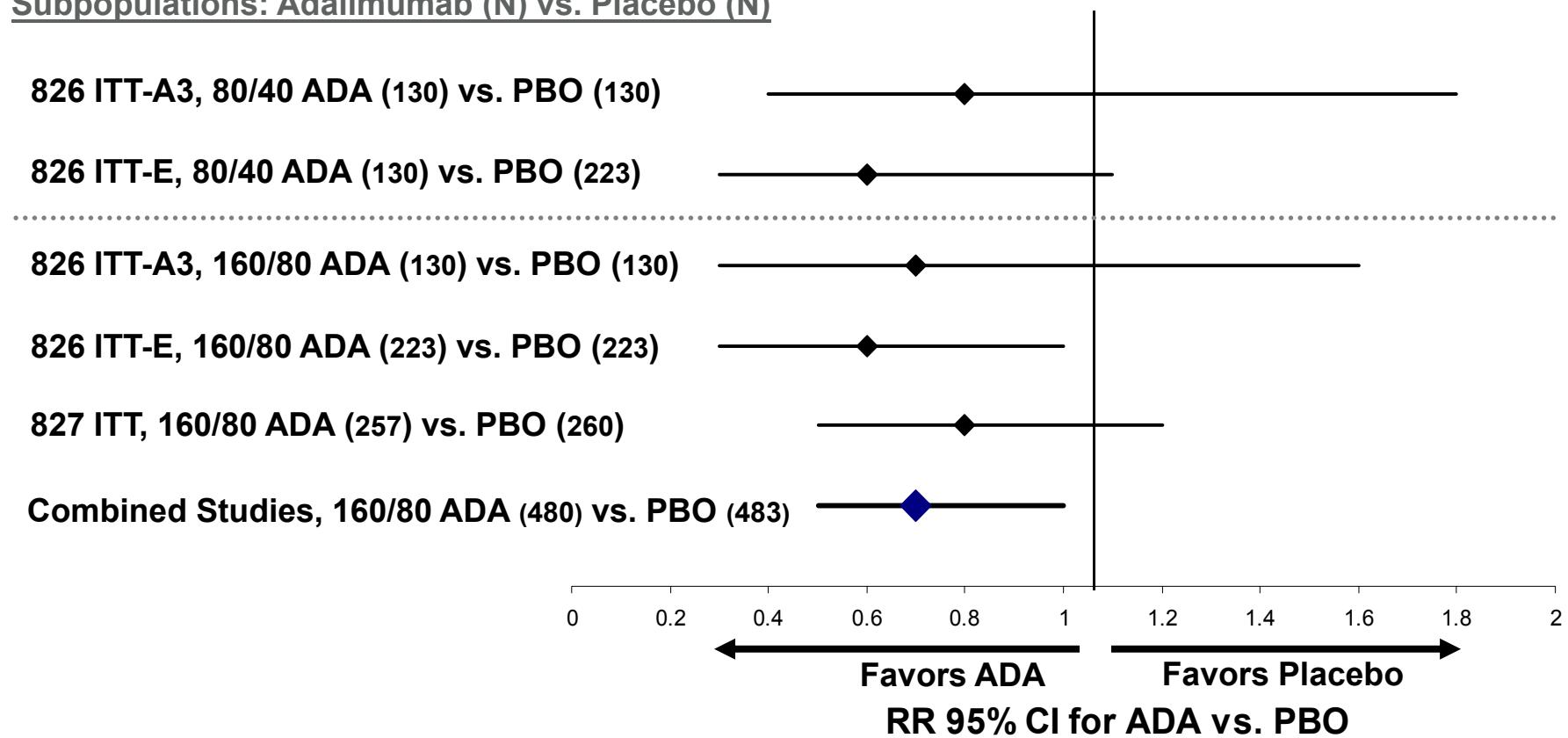
All-cause Hospitalizations

Subgroup Analyses

Weeks 0-52 Studies 826 and 827

All-cause Hospitalizations Relative Risk (Weeks 0-52)

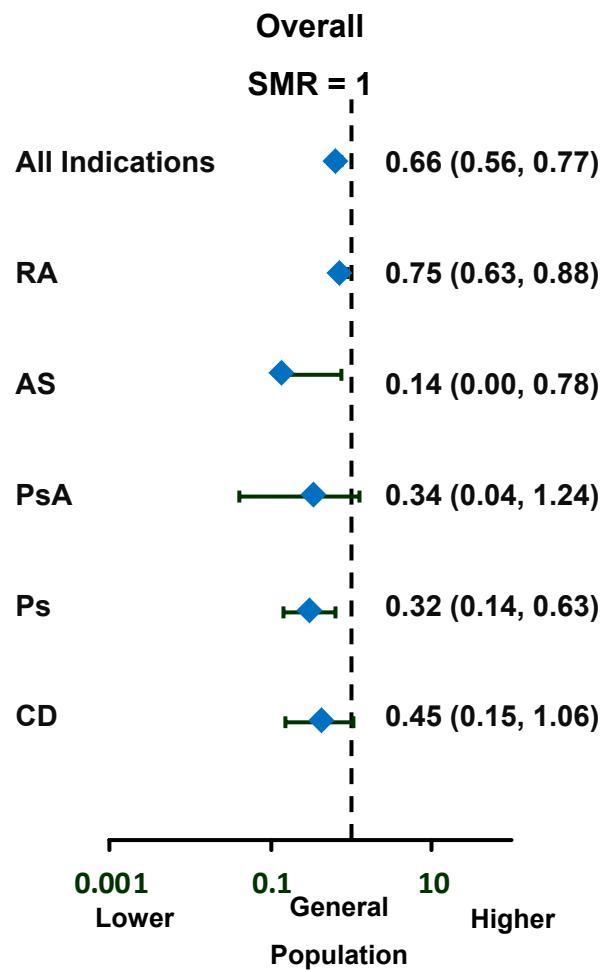
Subpopulations: Adalimumab (N) vs. Placebo (N)



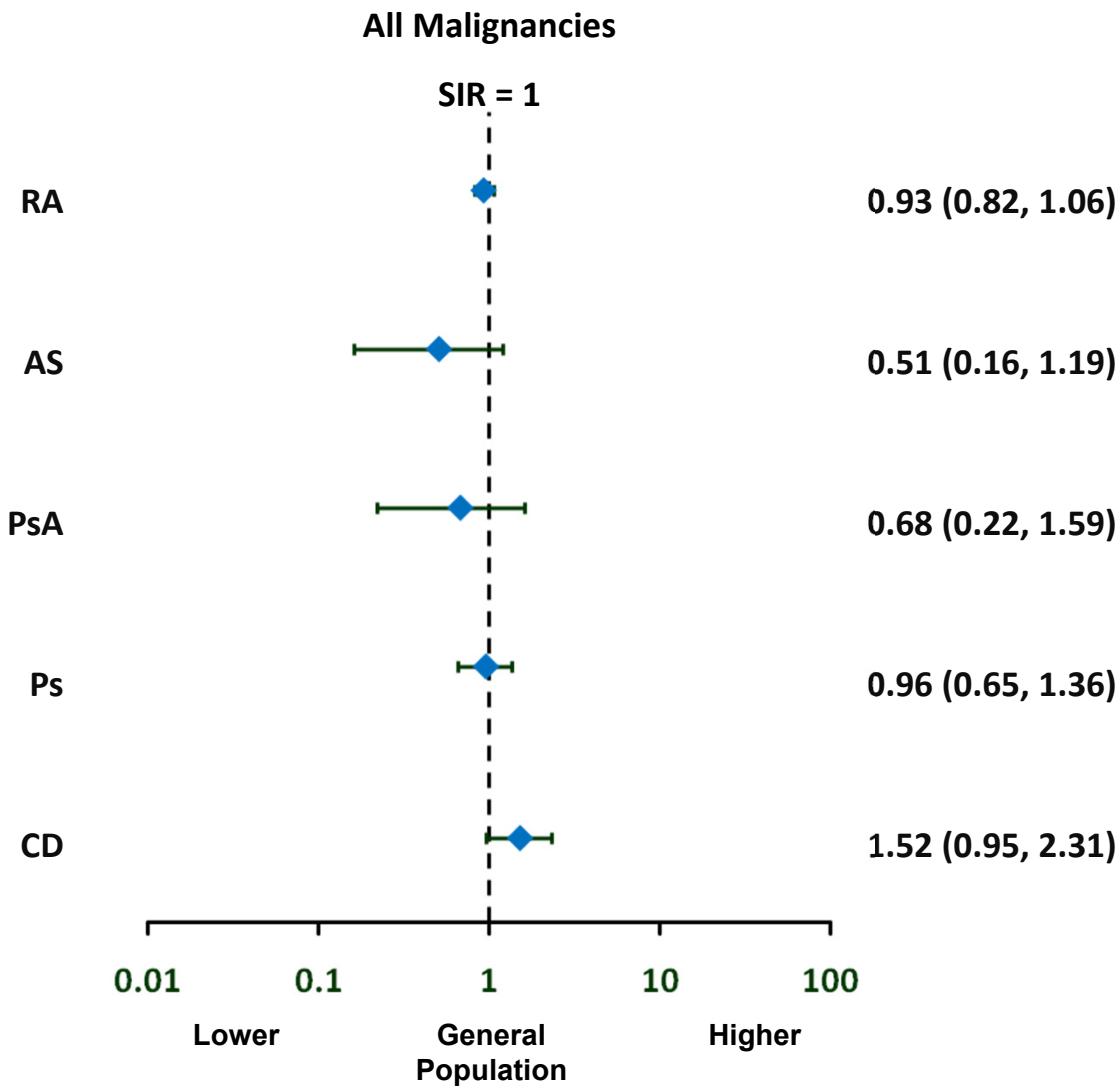
RR=relative risk

HP-069S

Standardized Mortality Rates Compared With the General Population



Standardized Incidence Ratios (SIR) for All Malignancies Excluding NMSC



Incidence Rates (E/100 PYs) of Serious Adverse Events of Interest

	Rheumatoid arthritis	Ankylosing spondylitis	Psoriatic arthritis	Psoriasis	Crohn's disease
N	14,109	1684	837	3010	3606
Exposure, PYs	23,942.6	1985.6	997.5	5061.8	4138.0
Serious infections	4.6	1.4	2.8	1.7	6.7
Active tuberculosis	0.3	0	0.2	0.1	<0.1
Opportunistic infections	<0.1	0	0	0	<0.1
Demyelinating disorder	<0.1	<0.1	0	0	0.1
Lupus-like syndrome	<0.1	0.1	0	0	<0.1
CHF	0.2	0.1	0	<0.1	0
New onset/worsening of psoriasis	<0.1	<0.1	0.1	<0.1	<0.1
Malignancies excluding lymphoma and NMSC	0.9	0.2	0.2	0.6	0.5
Lymphoma	0.1	<0.1	0.2	<0.1	<0.1
NMSC ^a	0.2	0.3	0.1	0.1	<0.1
Melanoma	<0.1	<0.1	0	0.2	0
Any AE leading to death	0.8	<0.1	0.3	0.2	0.1

AE, adverse event; CHF, congestive heart failure; NMSC, non-melanoma skin cancer; PYs, patient-years.

^aOnly serious NMSC events

Burmester GR, Panaccione R, Gordon KB, et al. Ann Rheum Dis (2012) .

Remission at Week 52

Study 827

Remission at Week 52	Placebo N=246	ADA 160/80 N=248	P-value ^a
Primary analysis using non-responder imputation (NRI)	8.5%	17.3%	0.004
Analysis using combination of NRI and multiple imputation ^b	10.7%	19.1%	0.009

^a P-value for the comparison of ADA versus placebo using the CMH test stratified by prior anti-TNF use (yes/no)

^b NRI imputation for patients who switched to OL or discontinued from the study due to lack of efficacy or UC disease flare prior to Week 52 and multiple imputation for all other patients with missing Week 52 Mayo score

Remission at Week 52

Study 827

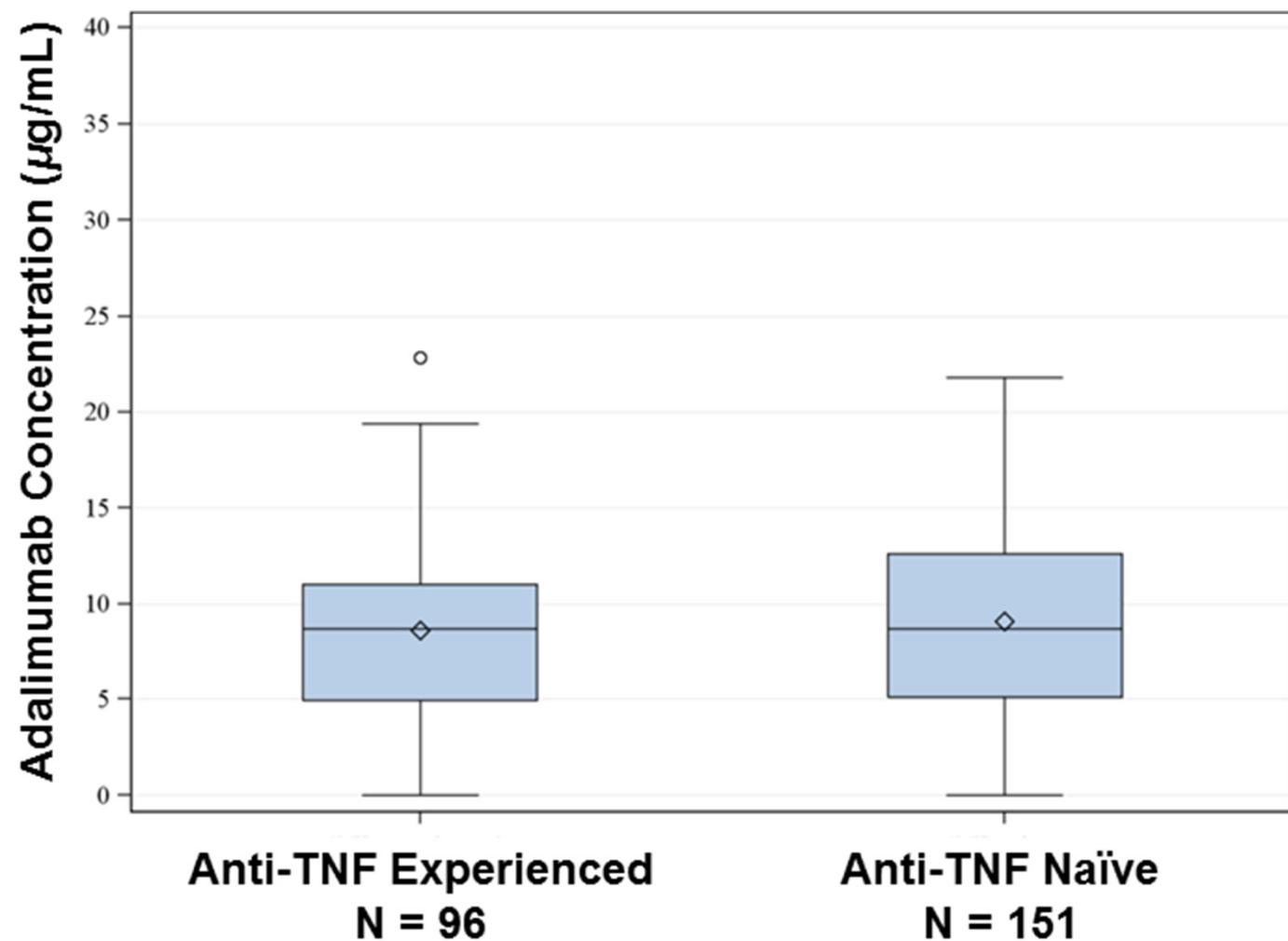
Combination of NRI and MI ^a	Number (%) of Patients		
	Placebo N = 246	Adalimumab 160/80 N = 248	P value ^b
Remission at week 8	9.5	16.7	0.020
Remission at week 52	10.7	19.1	0.009
Sustained remission at both weeks 8 and 52	4.4	8.8	0.056

^a NRI imputation for patients who switched to OL or discontinued from the study due to lack of efficacy or UC disease flare prior to Week 52 and multiple imputation for all other patients with missing Week 52 Mayo score

^b P-value for the comparison of ADA versus placebo using the CMH test stratified by prior anti-TNF use (yes/no)

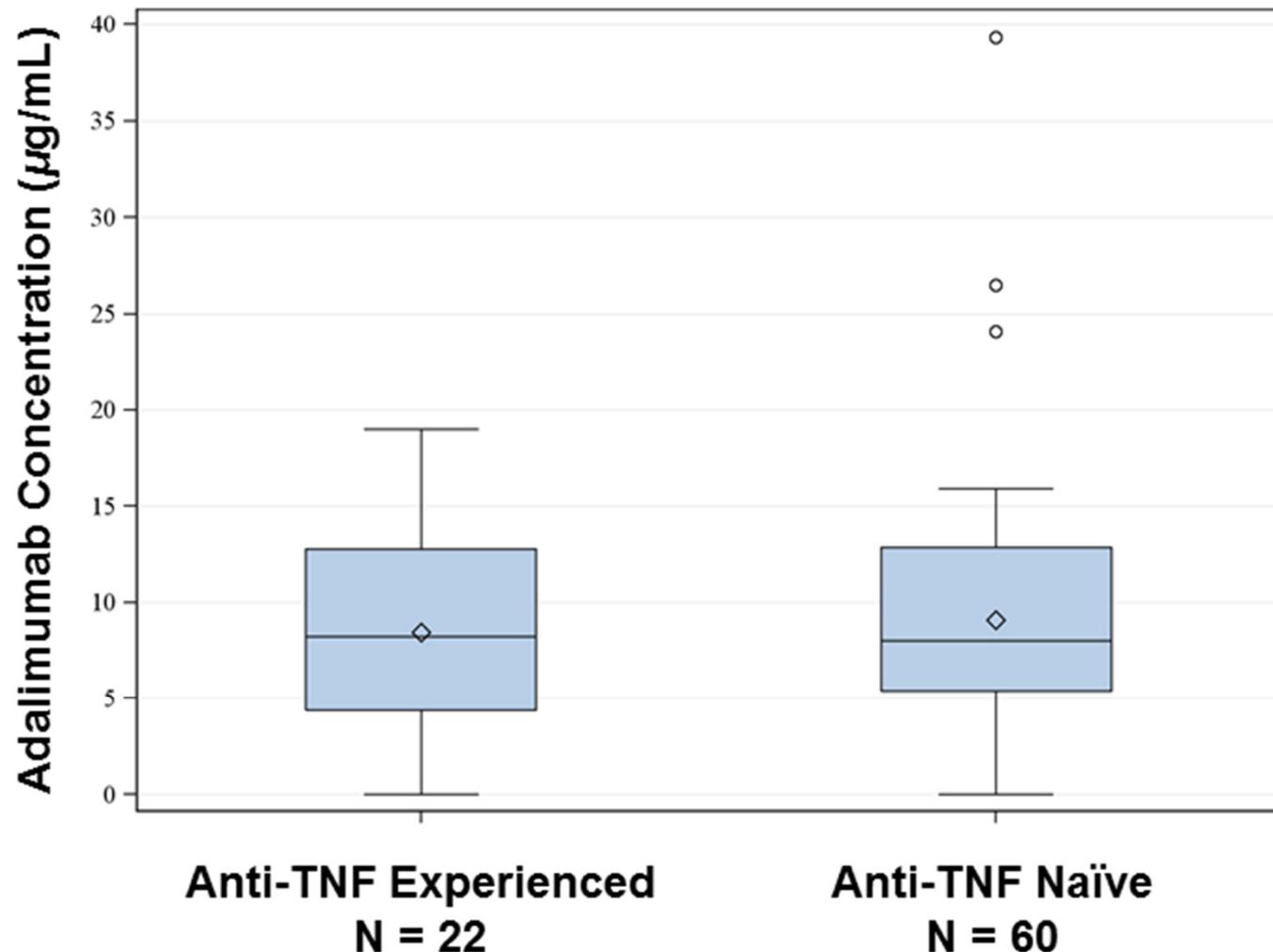
Adalimumab Concentration by Prior Anti-TNF Use

Study 827 - Week 8

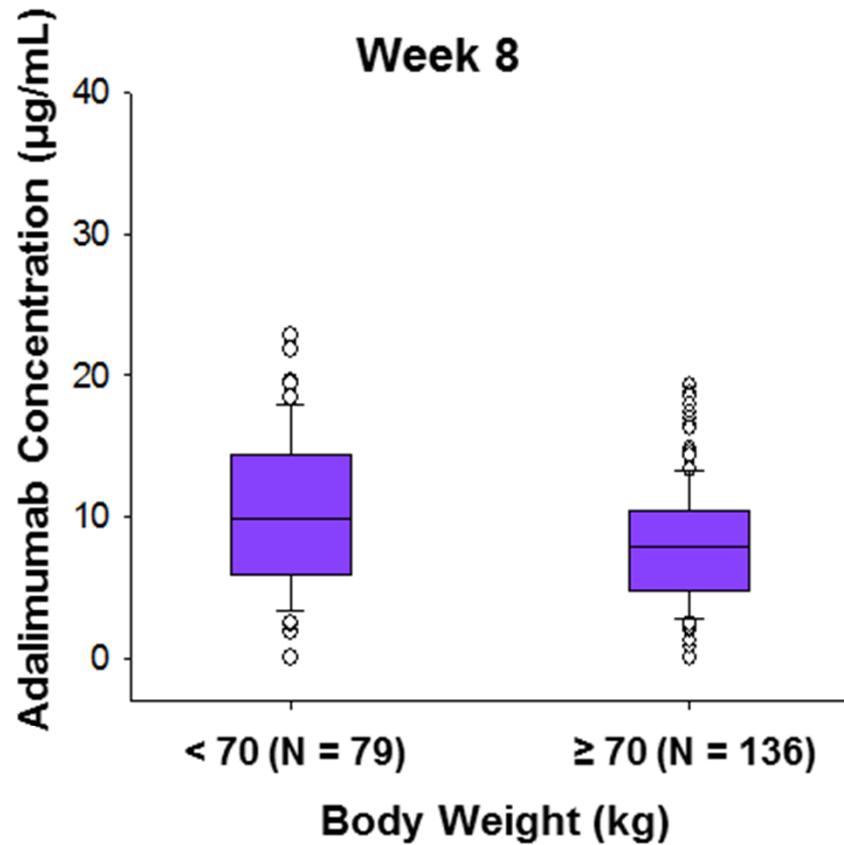


Adalimumab Concentration by Prior Anti-TNF Use

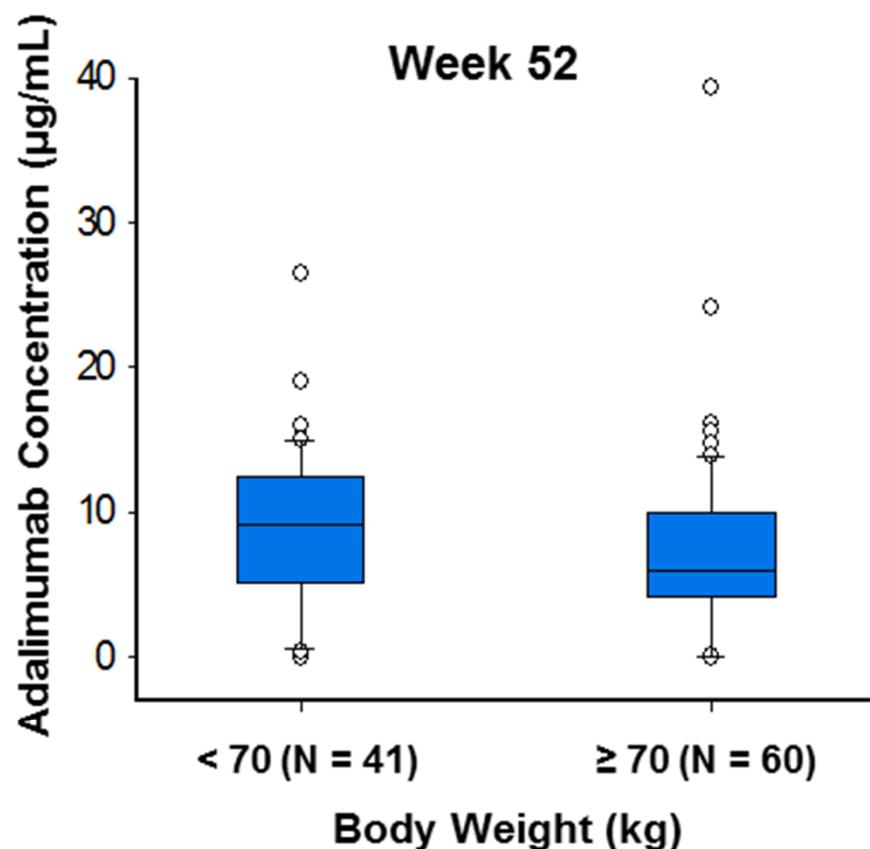
Study 827 - Week 52



Adalimumab Exposures by 70 kg Body Weight Cut-off in Study 827



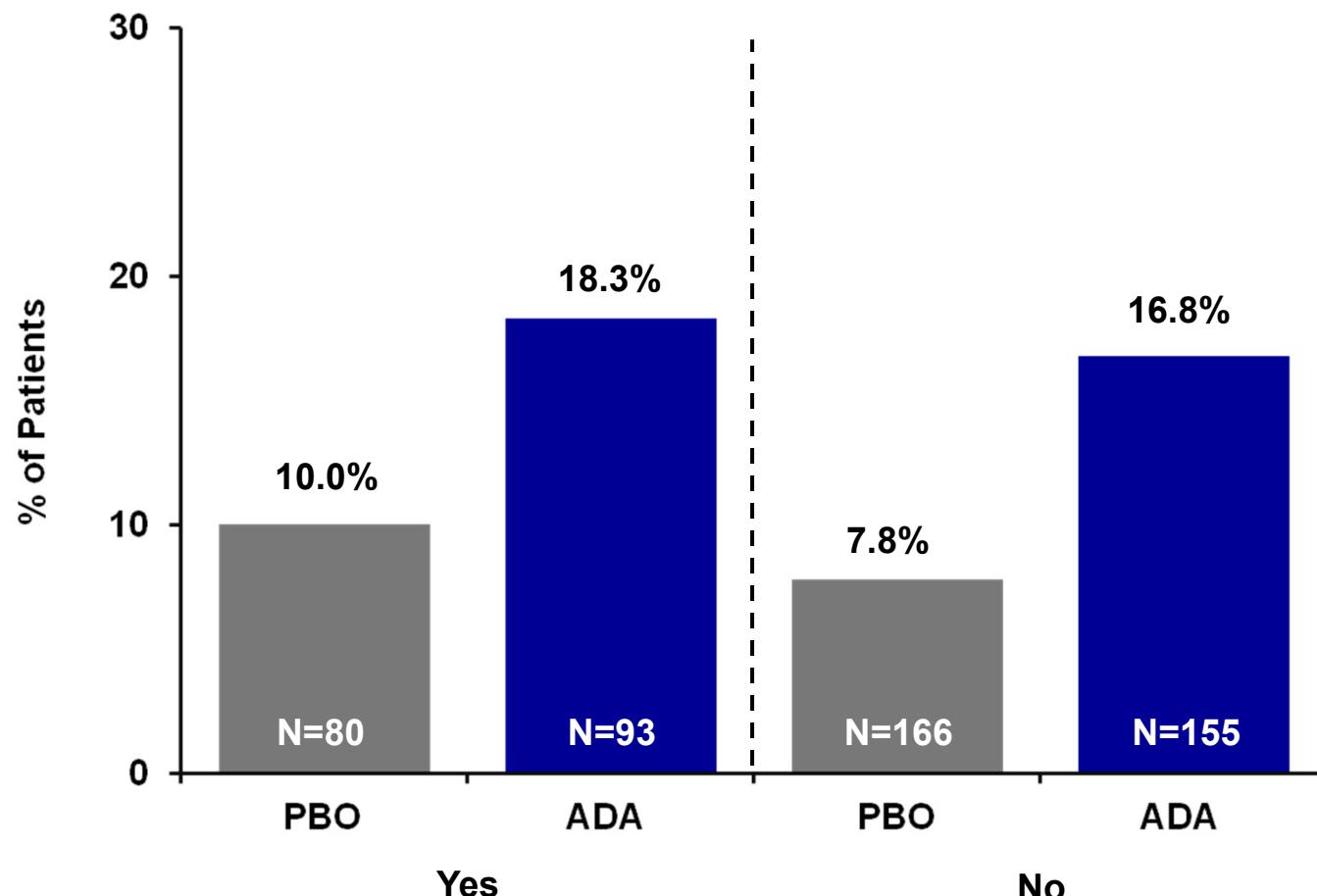
Solid line in the box plot = Median



For Week 52, only subjects who stayed on 40 mg eow were included in the plot.

Week 52 Remission by Baseline Immunosuppressant Use

Study 827



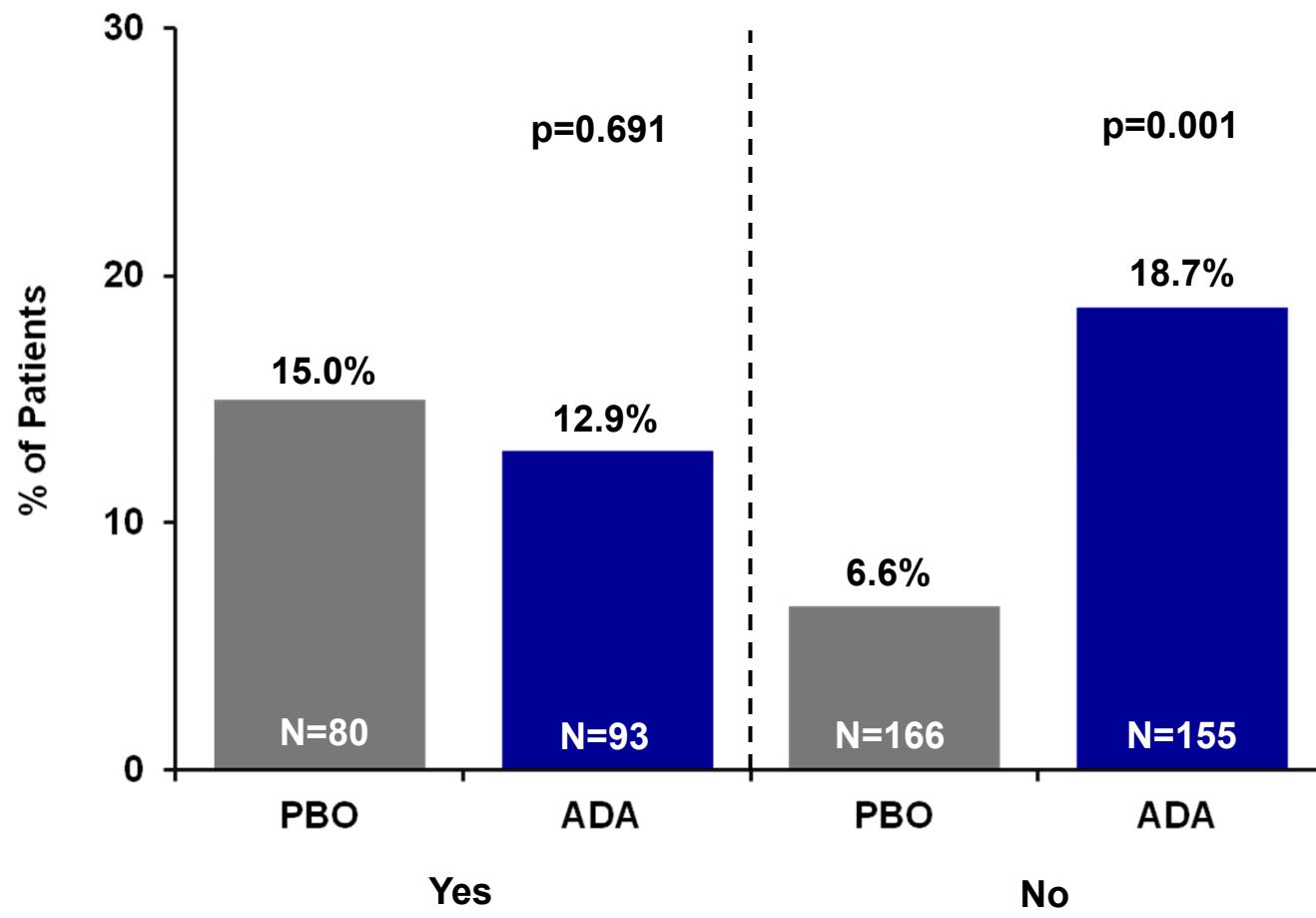
ITT analysis set

Immunosuppressant Use at Baseline?

EG-074S

Week 8 Remission by Baseline Immunosuppressant Use

Study 827

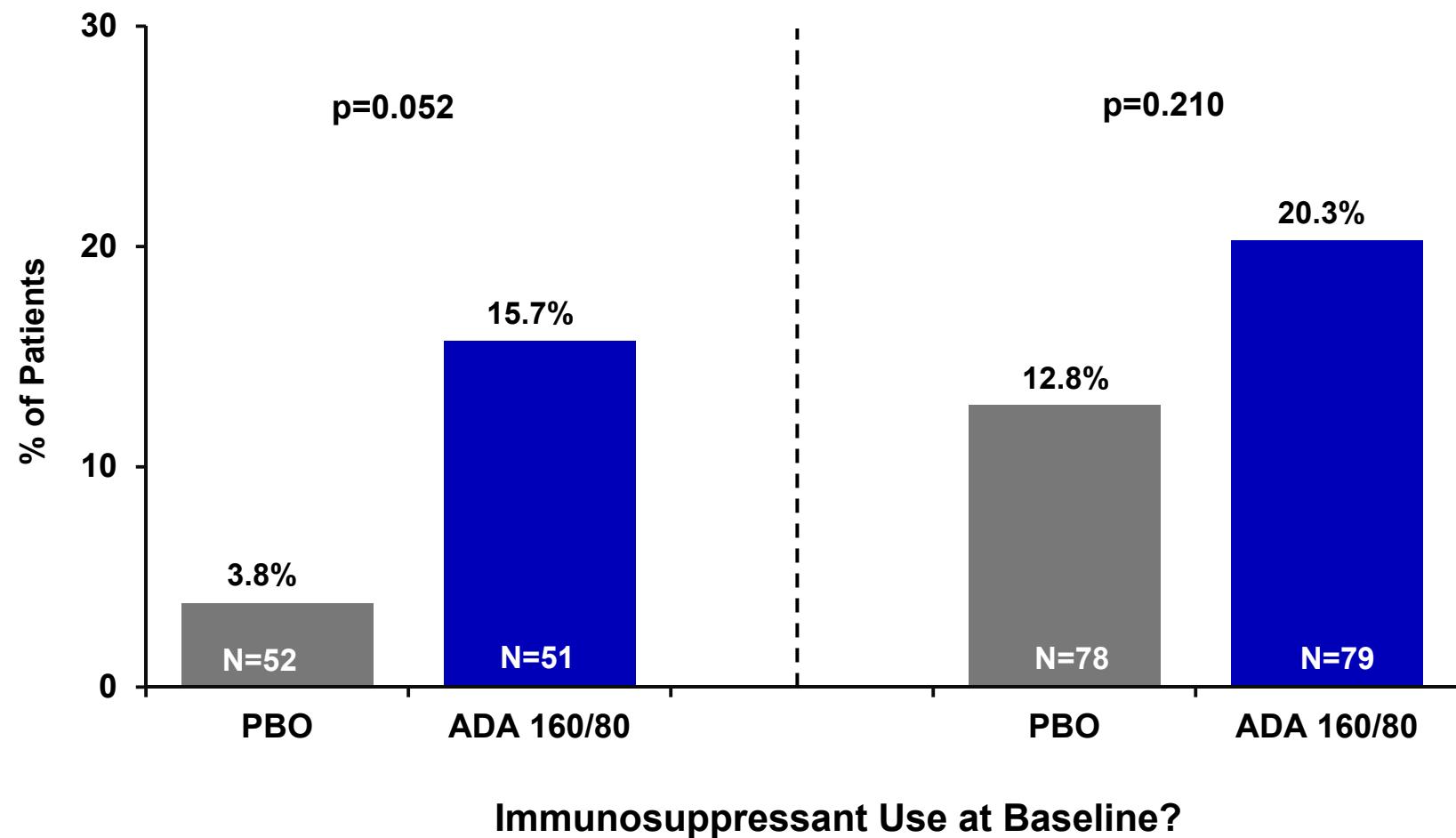


ITT analysis set

Immunosuppressant Use at Baseline?

EF-393S

Week 8 Remission by Baseline Immunosuppressant Use Study 826



ITT analysis set

Yes

No

EF-392S